Implications for the uptake of HIV and TB preventive therapies among HIV-positive pregnant women in South Africa

by

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Abstract

Of 33 million people living with HIV worldwide in 2015, one-third are estimated to be infected with *Mycobacterium tuberculosis*.[1] About 1.2 million new cases of tuberculosis (TB) occurred among people living with HIV (PLWH), which account 11% of all TB incidence cases.[1] HIV-positive pregnant women are a particularly relevant population for delivering preventive therapies for HIV and TB. In South Africa, over 30% of women who came to public antenatal clinics were HIV-positive in 2013.[2] Active tuberculosis during pregnancy increases not only the risk of maternal mortality but also infant adverse health outcomes.[3–5] Isoniazid preventive therapy (IPT) can reduce the risk of developing TB up to 60% among PLWH.[6] Thus to ensure better health outcomes for both infants and mothers, antiretroviral therapy (ART) for life-long period and IPT for at least 12 months are recommended to all HIV-positive pregnant women. However, the uptake of IPT has been slow around the world and retention in care and adherence rates significantly drop once delivery occurs.[7,8]

This thesis addresses the gaps in understanding patients' priorities and motivations to take preventive therapies in HIV-positive pregnant women. In a prospective cohort of 204 pregnant women recently diagnosed with HIV in Matlosana, South Africa, maternal priorities and motivation to take preventive therapies for HIV and TB were examined during the

antepartum and postpartum periods using stated preference methods. Factors at individual, interpersonal or health services levels and potential motivators that may influence patients' decisions to take preventive therapies were selected based on qualitative interviews and literature reviews. We also explored the cost-effectiveness of providing IPT to all eligible HIV-positive pregnant women without LTBI screening strategies.

Our findings suggest that women prioritize infants' health and concern for partners and family and may make medical decisions around these factors but also have high perceived benefits of medications for their own health. Universal IPT could be considered cost-effective compared to test-driven strategies. Incorporating these findings would be important to develop patient-centered interventions for enhancing the uptake of ART and IPT among HIV-positive pregnant women in South Africa and other similar settings with high TB and HIV burden.

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Contents

List of Tables

Chapter 3

Chapter 4

Chapter 5

Chapter 6

List of Figures

Chapter 2

Chapter 3

Chapter 4

Chapter 5

Chapter 6

CHAPTER 1

Introduction

1.1 Overview

Pregnancy is an important gateway to the health system in South Africa, and during the first antenatal care visits many women first learn that they are infected with HIV– a diagnosis that can initiate a cascade of medical decisions, including initiation of antiretroviral therapy (ART), testing for active and latent tuberculosis (TB), and if infected, isoniazid preventive therapy (IPT). Most women are unprepared for this diagnosis and for the rapid flood of healthcare interventions that follow. For ensuring their long-term health and that of their babies, it is critical to understand pregnant women's perception and preferences about preventive therapies for HIV and TB and to provide care in a way that is most acceptable to these women. The overall aim of this thesis was to examine maternal priorities and motivation to take preventive therapies among pregnant women recently diagnosed with HIV and to estimate the cost-effectiveness of providing IPT to all eligible HIV-positive pregnant women without latent TB infection (LTBI) screening. This section includes reviews of epidemiology of HIV and TB among pregnant women, challenges of uptaking preventive therapies and the overall significance of the thesis research.

1.2 Epidemiology of HIV and TB among pregnant women

It is estimated that about one-third of the 33 million people living with HIV (PLWH) are co-infected with *Mycobacterium tuberculosis* in 2015.[1] There were 1.2 million new cases of tuberculosis (TB) among PLWH.[1] TB accounts about 25% of all causes mortality among PLWH. The prevalence of HIV infection among adolescent women is 3-7 fold higher than among adolescent men in sub-Saharan Africa,[9] and women at the age of 15-49 years are at the greatest risk of developing active TB disease.[10] A study conducted in South Africa showed that the prevalence of LTBI among women at reproductive age could be as high as 84%.[11]

Many women first learn that they are infected with HIV during antenatal care (ANC) visits. A cross-sectional study in South Africa showed that about 37% of women who came to public antenatal clinics were HIV-positive, and of these 23% reported any symptom of TB in 2011.[12] The prevalence of TB in HIV-positive pregnant women in South Africa is similar to that of the general population as 795/100,000 but in some areas, HIV-positive pregnant women are at 10-fold increased risk of active TB compared to HIV-uninfected pregnant women.[5] Tuberculosis increases the risk of maternal mortality during pregnancy or postpartum period and infant adverse health outcomes.[3–5,13] Thus it is critical not only to actively find and treat TB cases but also to prevent conversion of latent TB infection to active TB disease.

1.3 Challenge of uptaking preventive therapies

During the first ANC visit, pregnant women are offered a series of tests including HIV counseling and testing, TB symptom screening and a Tuberculin Skin Test (TST) if TST is available.[14] TST is administered to detect the presence of Mycobacterium tuberculosis, the

bacterium that causes TB. Once tuberculin purified protein derivative (PPD) is injected into the inner surface of the forearm, the size of induration is measured after 48 to 72 hours to determine positivity of reaction. An induration of 5 or more millimeters is considered as positive in HIV-positive individuals and other high risk groups.[15]

The South African national guideline recommends that if a pregnant woman is newly diagnosed with HIV and has active TB symptoms, TB treatment would be started first, followed by ART as soon as possible and within 2-8 weeks. All HIV-positive pregnant women need to be initiated on a fixed-dose-combination pill (FDC), consisted of three drugs used in the first-line regimen (tenofovir, emtricitabine and efavirenz) and continue the therapy for a life-long period regardless of CD4 cell count.[14] The National TB programme (NTP) initially adopted the WHO's recommendation to provide 6-month IPT to all HIV-positive persons regardless of TST status in 2010 but re-introduced administration of TST in the updated 2014 guideline. Under the new guideline, TST is recommended to determine duration of IPT provision: 12 months if TST result is negative or unavailable or 36 months if TST is positive. Implementation of this guideline has been slow and challenging partially due to operational challenges of TST administration and stock outs of tuberculin.[16]

Another challenge is the cascade of HIV care after delivery among pregnant women. In a meta-analysis of ART adherence among high, middle and low-income countries, the proportion of pregnant women with adequate adherence (defined as taking >80% of pills) reduced from 76% during the prenatal period to 53% during the postpartum.[17] The initiation of and adherence to IPT are even lower.[18,19] Only 21% of countries and 14 of the 41 high burden TB/HIV countries reported the provision of IPT to HIV-positive people in 2013.[20] In the prospective cohort conducted in South Africa, 59% of patients who initiated IPT completed 6 months of IPT.[13] Recent study in Lesotho which evaluated the feasibility of

implementation of the IPT guideline in maternal and child health settings showed that 78.5% of HIV-positive women initiated IPT, and of whom, 65% completed 6 months of IPT.[21]

In the systemic review of qualitative data on factors associated with adherence to IPT among people living with HIV/AIDS, five main themes were identified: individual personal beliefs, HIV treatment issues, socio-economic factors, family and other social factors, and relationship with health providers.[22] Work commitment, side effects of isoniazid, HIV-related stigma as well as non-disclosure of HIV status were reported as the common reasons for non-adherence (i.e. defined as completing less than 80% of scheduled clinic visits for medicine refill).[23] Lack of clear guidance and training on IPT prescription among healthcare providers have also been reported as major barriers to implementation of IPT.[16]

1.4 Overall significance of the research

Barriers and facilitators of IPT uptake have been explored among patients and healthcare providers mostly in qualitative studies.[16,22] In this thesis, we examined maternal priorities and motivation among different attributes related to taking therapies. Implementation of therapies and interventions is often shaped by health care providers, researchers and policy makers but not by the patients who actually take the drugs. The discrete choice experiment (DCE) is a widely used method to understand how individuals may make trade-offs and prioritize among different attributes in decision making.[17-20] There has been increasing use of DCEs in health service researches to understand patients' buy-in for different therapies or interventions including HIV testing thus to improve patients' adherence and health outcome.[24–28] We expect that these results would inform policy makers, researchers and healthcare service providers to develop patient-centered strategies for

provision of preventive therapies in a way most acceptable to HIV-positive pregnant women in South Africa and other similar settings.

It is also important that IPT provision is implemented in a cost-effective way carefully weighting potential benefits and side effects of IPT to be expanded to all eligible HIV-positive pregnant women. Previous cost-effectiveness analyses of IPT have been mostly conducted in high-income and low/middle TB burden countries[29,30] and limited studies were focused in high TB burden settings.[31–34] A recent study in India reported that 6-months IPT regardless of CD4 cell counts would be cost-effective compared to IPT provision among those with CD4 cell counts <200 cells/mm^3 or no IPT at all among HIV-positive pregnant women. In South Africa, TST is often used to diagnose latent TB infection but it poses operational challenges as tuberculin needs to be refrigerated and patients are required to come back for reading the results. Studies have shown that up to 50% of patients may not return for TST reading thus losing the opportunity to initiate on IPT.[35] On the other hand, universally initiating all eligible individuals is subject to put more people without latent TB infection into treatment. Thus it is crucial to assess the feasibility and cost-effectiveness of providing IPT with and without different LTBI screening strategies in this population.

1.5 Overview of dissertation

This dissertation uses the methods and approaches from different disciplines including epidemiology and health economics. A total of 204 pregnant women completed the surveys to elicit priorities relating to ART and IPT during pregnancy and were followed up at the 14 weeks postpartum visit. Paper 1 and 2 used a survey instrument of stated preference method called best-worst scaling which allowed to elicit the ranking of the relative importance of 11 attributes related to uptaking ART and IPT. The attributes included treatment benefits for

maternal and infant heath, interpersonal support, trust in healthcare services, and structural barriers. Paper 3 used a conjoint analysis to understand maternal motivation to take preventive therapies. Trust in healthcare providers and medication benefits for having a long life were most highly prioritized in both antepartum and postpartum periods (Paper 2). Prevention for infants' illness was slightly more prioritized in the postpartum, and such increase in priority was associated with IPT provision at enrollment. However, participants expressed significantly greater difficulty in daily adherence to medications in the postpartum. When maternal motivation to take preventive therapies was examined, keeping them from giving HIV to their partners and keeping them healthy for their family were most prioritized in the antepartum but such prioritization decreased in the postpartum (Paper 3). Providing IPT all eligible HIV-positive pregnant women can be cost-effective especially if operational challenges of latent TB screening strategies prevent people to be initiated for IPT (Paper 4).

These results suggest that women prioritize infants' health and concern for partners and family and may make medical decisions around these factors in the antepartum period but they also have higher perceived benefits for medication for their own health in the postpartum. Interventions to reinforce positive benefits of preventive therapies as well as counseling and support to encourage adherence can be an effective strategy to increase uptake of preventive therapies especially in the postpartum.

CHAPTER 2

Methods

2.1 Study context

This prospective study was nested within an ongoing randomized study to compare the performance of QuantiFERON®-TB In-Tube test (QGIT) to the routine tuberculin skin test (TST) in 14 South African clinics for detection of latent TB infection and linkage to treatment among individuals newly diagnosed with HIV.[36] For the parent study, study participants were recruited from 9 clinics located in the Matlosana subdistricts and 5 clinics in the Tlokwe subdistrict of the Dr. Kenneth Kaunda district in the North West Province (Figure 2.1). There are about 400,000 inhabitants in the City of Matlosana with 41.3% residing in Klerksdorp/Jouberton townships.[37] Klerksdorp is located approximately 170km South West of Johannesburg and has its neighboring township of Jouberton, Stilfontein, Orkney, Kanana and Khuma with mix of rural and urban population. The main economic activities are mining of gold and platinum group metals and agriculture. Tlokwe is smaller with about 163,000 inhabitants with 128,353 residing in Potchefstroom which hosts five tertiary institutions and 30 schools as an academic city. Potchefstroom is located at 45 km northeast of Klerksdorp.

The study team was based at the regional office of Perinatal HIV Research Unit (PHRU) in the Klerksdorp Tshepong hospital Complex (KTCH), one of the two public sector hospitals in the district. Since each clinic has different catchment area for source population, we recruited participants from all 14 clinics to have a representative population of these regions.

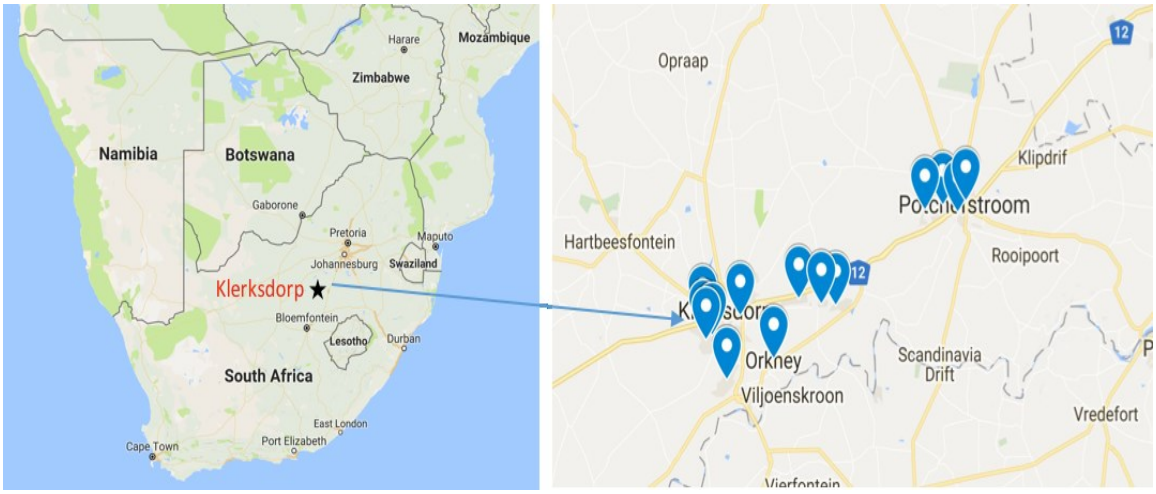

Figure 2.1. The location of 14 clinics in Matlosana and Tlokwe subdistricts in Dr. Kenneth Kaunda, North West Province, South Africa.

2.2. Study population and design

All HIV-positive pregnant women ≥ 18 years of age attending any of the 14 clinics between November 2014 and October 2015 were eligible to be enrolled into the study if they were newly diagnosed of HIV within 6 months and eligible to receive ART or IPT according to the South African guidelines. Since a part of the study questionnaires required participants to read written statements, participants who were not able to read a written sample sentence were excluded but we offered questionnaires in four most widely used languages in this region (English, Setswana, Zulu and Xhosa). We have not included the gestation week as the criteria since the timing of 1st ANC visit might be associated with maternal preferences and

potentially adherence rate in the postpartum period thus itself is an interest as a research question.[27] During ANC visits, clinicians referred pregnant women newly diagnosed of HIV to study counselors, and eligible pregnant women were consented at a private counseling room and enrolled into the study. Each interview lasted for approximately 45 minutes.

In South Africa, routine postnatal visits for infants and mothers are scheduled at 3 days, 6, 10, 14 weeks and 4, 5, 6, 9 and 12 months after delivery. We initially proposed to conduct two follow-up visits at 6 and 14 weeks postpartum. However, many of the study participants presented at either of 6 or 14 weeks visits. Since we expected that delivery itself would be the defining event to shape maternal priorities and changes in maternal priorities between 6 and 14 weeks might be less significant, we analyzed the data at 14 weeks visit as the primary visit and 6 weeks visit or the visit completed after 14 weeks in the postpartum was included if participants missed the 14 weeks visit. Characteristics at baseline and follow-up visits were compared by the type of visits (6, 14 or >14 weeks visits) to ensure compatibility across different types of visits.

During the follow-up visits, maternal and infant clinical information was obtained including infant's HIV status. The HIV polymerase chain reaction (PCR) test was performed at the 6 weeks visit to determine HIV infection status of an infant. The national guideline updated in April 2015 recommended to perform HIV PCR tests at 10 weeks, which is four weeks after stopping 6-weeks Nevirapine (NVP) prophylaxis.[38] Thus all infant HIV status was recorded at the 14 weeks postpartum visit. Maternal self-reported adherence to ART and IPT was measured by the AIDS Clinical Trials Group (ACTG) Adherence Questionnaire, which is based on 4-day recall with five items. This questionnaire has been extensively used and validated in other studies.[39–42] Adherence to IPT was also measured by testing eligible participants' urine samples by IsoScreen kit (GFC Diagnostics Limited, Oxfordshire, UK), a test to measure the presence of INH metabolites over the past 24-48 hours. Maternal priorities and

motivations related to preventive therapies were measured at both enrollment and postpartum visits using the same stated-preference instruments, which will be explained in the following section.

2.2 Assessment of patient preferences and priorities using conjoint analysis and best-worst scaling

2.2.1. Definition of patient preferences and application in health research

Although there may not be a consistent definition, patient preferences can be defined as a patient's value or desirability for health care choices to health state, intervention or treatment.[43,44] In the field of health service research, methods to quantify preferences can be categorized into two ways: 1) indirect elicitation using trade-offs such as ranking, rating, or choice designs or 2) direct elicitation of monetary values of an intervention including contingent valuation, standard gamble, or willingness-to-pay methods.[24] These methods have been previously used to understand issues of patient adherence and other health-related outcome and applied as alternative sources of utilities.[24] The most common types of choice designs used to elicit preferences in healthcare research are conjoint analysis, which is often referred as discrete choice experiments (DCE)[24], and more recently best-worst scaling (BWS) method.[45,46] In the following section, detailed theoretical background of these two methods is provided.

2.2.2. Theoretical background of best-worst scaling and conjoint analysis

In economics or marketing research, eliciting an individual's preferences for goods or services can be categorized into two types: 1) revealed preferences, which are examined by

observing the actual decisions an individual makes, or 2) stated preferences where an individual's intention for behaviors are elicited in hypothetical situations.[47] The most common type of conjoint analysis is the discrete choice experiment (DCE), which has been widely used in transportation and environmental research to elicit individuals' preferences and predict behaviors.[48,49] Recently, DCEs have been applied in health services research for various purposes including elicitation of patients' or providers' views on diagnosis, treatment or access to services. DCEs typically require respondents to make a choice over sets of hypothetical alternatives in repeated choice sets (i.e. scenarios) where each alterative is described by several characteristics (i.e. attributes). DCEs allow to quantitatively evaluate the relative importance of different attributes.[50]

Best-worst scaling (BWS) method was devised by Finn and Louviere (1992) and introduced to healthcare research by McIntosh and Louviere (2002).[45,51] Unlike in DCEs where a respondent need to compare multiple characteristics between two choice sets simultaneously, BWS requires each respondent to choose one best and one worst option in a given profile. It is assumed that picking up extremes is easier than ranking all alternatives and give less cognitive burden compared to DCEs. BWS is grounded on Random Utility Theory (RUT), which is based on the assumption that every individual is a rational decision-maker thus makes choices to maximize underlying utility within a choice set. The statistical and measurement properties of BWS were recently proved although its characteristics still need further statistical evidence and rigorous tests.[52]

In the random utility model, each person's choice is comprised of two components, the observed characteristics, v_{ij}, and a stochastic error component, ε_{ij}. Thus utility (u_{ij}) can be expressed as following for individual i and attribute j:

$$u_{ij} = x_{ij}\beta + \varepsilon_{ij} = v_{ij} + \varepsilon_{ij}$$

where v_{ij} is the systematic part and ε_{ij} is the random error term of utility. The main assumption of the model is that the ε_{ij} is iid random variable from Type-I-Extreme-Value (T1EV) function which is defined as:

$$f_{\varepsilon_{ij}} = e^{-e^{-\varepsilon_{ij}}} e^{-\varepsilon_{ij}}$$

The random error term cannot be observed for each individual; however, we predict the patterns of choices over many individuals and choice occasions, which provide the probability P_{ij} of individual i choosing product j from a set of given products as following:

$$\begin{aligned} P_{ij} &= \Pr[u_{ij} > u_{ik}] = \Pr[v_{ij} + \varepsilon_{ij} > v_{ik} + \varepsilon_{ik}] \\ &= \Pr[v_{ij} - v_{ik} + \varepsilon_{ij} > \varepsilon_{ik}] \text{ for } all\ k \neq j \end{aligned}$$

If we know ε_{ij}, then we know the choice probability P_{ij} is conditional on this information. If we rewrite $\beta_k = v_{ij} - v_{ik} + \varepsilon_{ij}$ then the conditional probability, $P_{ij|\varepsilon_{ij}}$ is:

$$\begin{aligned} P_{ij|\varepsilon_{ij}} &= \Pr[\varepsilon_{ik} < \beta_k, \text{for all } k \neq j] \\ &= \Pr[\varepsilon_{i1} < \beta_1] \cdot \Pr[\varepsilon_{i2} < \beta_2] \cdot \ldots \cdot \Pr[\varepsilon_{ij} < \beta_j, \text{for all } k \neq j] \\ &= e^{-e^{-\beta_1}} \cdot e^{-e^{-\beta_2}} \cdot \ldots \cdot e^{-e^{-\beta_j}} \\ &= \prod_{k \neq j} e^{-e^{-\beta_k}} \end{aligned}$$

Although we do not know the value of the random error, ε_{ij}, we know that ε_{ij} follows T1EV density. Using Bayes' Theorem and the known T1EV density function,

$$P_{ij} = \int_{-\infty}^{\infty} P_{ij|\varepsilon_{ij}} \cdot f_{\varepsilon_{ij}}\, d\varepsilon_{ij} = \int_{-\infty}^{\infty} \left(\prod_{k \neq j} e^{-e^{-\beta_k}} \right) \cdot e^{-e^{-\varepsilon_{ij}}} e^{-\varepsilon_{ij}}\, d\varepsilon_{ij}$$

$$= \int_{-\infty}^{\infty} \left(\prod_{k=1}^{J} e^{-e^{-\beta_k}} \right) e^{-e^{-\varepsilon_{ij}}} \cdot e^{-\varepsilon_{ij}} \cdot e^{-e^{-\varepsilon_{ij}}}\, d\varepsilon_{ij}$$

$$= \int_{-\infty}^{\infty} \left(\prod_{k=1}^{J} e^{-e^{-\beta_k}} \right) e^{-\varepsilon_{ij}} d\varepsilon_{ij}$$

$$= \int_{-\infty}^{\infty} exp\left(-\sum_{k=1}^{J} e^{-\beta_k} \right) e^{-\varepsilon_{ij}} d\varepsilon_{ij}$$

$$= \int_{-\infty}^{\infty} exp\left(-\sum_{k=1}^{J} e^{-(v_{ij} - v_{ik} + \varepsilon_{ij})} \right) e^{-\varepsilon_{ij}} d\varepsilon_{ij}$$

$$= \int_{-\infty}^{\infty} exp\left(-e^{-\varepsilon_{ij}} \sum_{k=1}^{J} e^{-(v_{ij} - v_{ik})} \right) e^{-\varepsilon_{ij}} d\varepsilon_{ij}$$

If we put Q = $\sum_{k=1}^{J} e^{-(v_{ij} - v_{ik})}$ and $y = e^{-\varepsilon_{ij}}$, then the choice probability can be written as

$$P_{ij} = \int_{0}^{\infty} exp(-yQ) \cdot y \; |J| dy = \int_{0}^{\infty} exp(-yQ) \cdot dy = \left[\frac{-1}{Q} e^{-Qy} \right]_{0}^{\infty} = \frac{1}{Q}$$

$$= \frac{1}{\sum_{k=1}^{J} e^{-(v_{ij} - v_{ik})}} = \frac{e^{v_{ij}}}{\sum_{k=1}^{J} e^{v_{ik}}}$$

which shows that the probability for an individual *i* to choose an alternative *j* follows

the logit model for the choice probabilities. When there are more than two alternatives, the model follows multinomial logit (often called as conditional logit). Where there are only two alternatives, it becomes binary logit and requires key assumption of independent distributions of the error terms. The systematic component of utility follows a linear function of parameters, resulting in the logit choice probability model as shown above. Thus DCE and BWS experiments with two or more options are often analyzed by conditional logistic regression in the exploded dataset where each question is treated independently. In conditional logistic regression, beta coefficients are estimated using maximum likelihood estimation and can be interested as **preference or utility weights for given attributes.**

Another assumption of BWS is that the utility of each attribute being chosen as the worst attribute is the negative of being chosen as the best attribute. This property was mathematically proved by Marley and Lourivere (2005).[52] A complete set of best and worst choice probabilities on a finite set T satisfies a consistent random utility model provided it satisfies a random utility model with a common set of random variables $U_z, z \in T$, such that for $r, s \in T, r \neq s, B_z = -W_Z = U_z$. The probability of maximizing the utility follows the standard results of logit formula. There are different assumptions about the process of making best and worst choices. The mostly widely accepted assumption is that a respondent chooses the best option first, followed by the worst option in a choice set (i.e. sequential best-worst model). In this study, I adopted the sequential best-worst model for the analysis.

Conditional logit assumes that the subjects' preferences for the attributes and levels are homogenous across the population thus the probability of choosing a choice only depends on the systematic portion.[53] It also assumes that the ratio of probabilities of individuals choosing between two alternatives does not depend on the availability or attributes of the other attributes, which is referred as the assumption of independence from irrelevant

alternatives (IIA). When IIA assumption doesn't hold, the conditional logit models may incorrectly estimate the model outcome. Recently, there have been various approaches to relax such assumptions by using a mixed logit (random effects) model or a latent-class model or in combination of both methods.[54] Unlike in conditional logit where it estimates mean preference weights for the study sample, a mixed logit model assumes that there is individual heterogeneity and allow coefficients to vary across individuals. Thus the mixed logit model measures both mean preference weights and their expected distribution across the sample[55] and provide distributions for both mean preferences weight and standard errors. In Chapter 5, the DCE experiment was analyzed using mixed logit models.

2.3 Instrument design and development

This study adopted the framework suggested for instrument development of a choice experiment:1) evidence synthesis, 2) expert consultation, 3) stakeholder engagement, 4) pretest interviews, and 5) pilot testing.[56] Qualitative interviews were previously conducted as part of the parent study, and the results were presented elsewhere.[57] Briefly, one male and one female participant were recruited from each of the 14 study clinics. In-depth, one-on-one interviews were conducted in English by a trained qualitative interviewer in a semi-structured format. Interviews lasted approximately one hour and were audio recorded and transcribed. Data analysis was carried out using ATLAS.ti 7.0 qualitative data analysis software (Berlin, Germany).

Key ideas were identified and coded using interpretive phenomenological analysis (IPA).[58] The codes derived from IPA were compared to the case summary findings which summarized a given participant's views and experiences on the key priori domain. The codes derived from IPA were classified into four superordinate themes under which three to four

subcategories were identified. Other barriers, facilitators or motivations to take preventive therapies among HIV-positive pregnant women were additionally identified from literature review. The attributes were selected and refined in repetitive process during expert consultations. Once the questionnaire was developed, it was pretested among study staff at local sites to ensure cultural competency and face validity of the questions. The final questionnaire was pilot tested among eligible potential patients at local clinics. We updated and refined the questionnaire based on the feedbacks.

Two types of choice experiments were developed. For paper 1 and paper 2, best-worst scaling object case (case 1) was used where a total of 11 objects related to preferences and characteristics of mothers and infants were elicited based on key informant interviews and literature reviews. For paper 3, 2^k factorial design was used with seven attributes, each attribute with two levels. Since we cannot estimate all 2^7 combinations, eight combinations were generated using design generators in a main-effects orthogonal design to ensure statistical independence among the factors.[59] Each attribute appeared for an equal number of times to minimize the variance in the parameter estimates. More details and examples of instrument designs are provided in each chapter.

CHAPTER 3

Prioritizing maternal perceptions of preventive therapies for tuberculosis among HIV-positive pregnant women using best-worst scaling

Hae-Young Kim, Colleen F. Hanrahan, David W. Dowdy, Neil Martinson, Jonathan Golub, John F P Bridges

3.1 Abstract

The uptake of isoniazid preventive therapy (IPT) has been slow among pregnant women living with HIV. We aimed to quantify priorities related to isoniazid preventive therapy (IPT) among pregnant women with HIV. We surveyed pregnant women recently diagnosed with HIV in 14 South African primary health clinics. Best-worst scaling (BWS) was used to elicit the priorities of 11 attributes related to preventive therapies. BWS scores were calculated based on the frequency of participants' selecting each attribute as the best or worst among five options (across multiple choice sets) and rescaled from 0 (always selected as worst) to 100 (always selected as best). Conditional logit models were used to assess differences by IPT status. Among 204 women surveyed, 64 (31%) were receiving IPT at enrollment. Trust in healthcare providers was given the highest priority (BWS score=73.7±0.9) followed by living a long life (BWS=67.5±0.9). Fear of disclosure of HIV serostatus to daily pill-taking was least prioritized (BWS=28.3±0.9). BW scores differed by IPT status for a few attributes, but overall ranking of attributes was similar (spearman's rho=0.9). Interventions to build trust in healthcare providers and to emphasize benefits of preventive treatment may enhance IPT uptake through a patient-centered approach.

3.2 Introduction

There were 10.4 million new cases and 1.4 million deaths from tuberculosis (TB) globally in 2015.[1] South Africa in particular has some of the highest rates of HIV and TB among pregnant women among whom HIV seroprevalence was about 30% in 2013.[2] Active TB case finding at antenatal care (ANC) clinics in rural South Africa showed that over 20% of HIV-positive pregnant women had at least one symptom of TB at ANC visits.[2] TB increases maternal mortality during pregnancy and the postpartum period as well as the risk of mother-to-child HIV transmission and infant outcomes among HIV-positive women.[3,35]

National Guidelines in South Africa recommend all HIV-positive pregnant women be initiated and continued on lifelong antiretroviral therapy (ART) and receive isoniazid preventive therapy (IPT) for up to 36 months to reduce TB incidence and mortality.[20,60] The integration of TB and HIV services in ANC clinics has been strongly promoted in Sub-Saharan Africa.[61] Only 9 of the 30 high-burden TB/HIV countries reported provision of IPT in 2015, and the coverage of IPT among people living with HIV (PLWH) is highly variable, ranging from 2% to 79%.[1] Over-reporting of IPT initiation has been reported in South Africa,[62] and of those who initiated IPT, the completion rate has been low.[18,19] A recent study in Lesotho showed that 78.5% of HIV-positive pregnant women initiated IPT, and of these, 65% completed their six-month course.[21]

Several factors are associated with low uptake of IPT among PLWH such as fear of side effects, non-disclosure of HIV status or competing socioeconomic responsibilities.[23] Among pregnant women with HIV, earlier gestational age at the first antenatal visit and initiation of antiretroviral treatment (ART) were associated with higher rates of IPT initiation.[21] However, many studies did not report pregnant women as a separate group, and

some studies excluded pregnant women altogether. Pregnant women may have different priorities and concerns that affect their decision-making related to IPT, and understanding their perspectives is important to deliver services in a most acceptable way. We sought to quantify the preferences that may encourage or discourage HIV-positive pregnant women to initiate IPT during pregnancy.

3.3 Methods

3.3.1 Study population and setting

We recruited HIV-positive pregnant women from 14 primary care public health prenatal clinics in the Dr. Kenneth Kaunda health district in the North West province, South Africa from January 2015 to December 2015. This study was nested within an ongoing cluster randomized trial in the same 14 clinics, which compares proportions with known TB infection status and IPT initiation among newly diagnosed HIV patients in clinics using two different diagnostic tests for latent TB infection.[36,57] Clinics were chosen to cover a range of patient volumes, urban vs rural setting, geography and clinic hours. Patients were eligible for enrolment if they were ≥18 years old, newly diagnosed with HIV in the preceding six months, and able to read either English, Xhosa, Setswana or Zulu. We sought to enroll all eligible pregnant patients during the study period. The percentage of enrollment was calculated based on the number of eligible patients as reported in the District Health Information System (DHIS) between January to July 2015, when the DHIS data was available.[63] The study was approved by the institutional review boards at the Johns Hopkins School of Medicine and University of Witwatersrand.

3.3.2 Study design

We conducted a cross-sectional survey incorporating a best-worst scaling (BWS) instrument (Case 1). BWS (Case 1) is a stated-preference method which allows for ranking of the relative importance of a list of attributes in a continuous quantitative scale, and has been increasingly used in healthcare research to understand patients' perspectives and preferences.[64] BWS asks the respondent to choose the best and the worst attribute from a set of available options in a given choice task, assuming that participants choose a best-worst pair maximizing the difference in the underlying utility.[52,56,65,66]

3.3.3 Selection of attributes

Through literature review, and prior in-depth interviews about patients' experiences and perceptions of ART and IPT, which were conducted as part of a qualitative sub-study of the parent study,[57] we identified attributes likely to influence women's decision-making regarding uptake of preventive therapies.[22,23,67] Four different themes were identified: treatment benefits for maternal and infant heath, interpersonal support, trust in healthcare services, and structural barriers. A total of 11 attributes were chosen, including roughly equal numbers of potential barriers and facilitators for initiation of IPT (Table 1). Attributes were converted to simple statements, which were then reviewed and refined by clinical experts and healthcare providers in the clinics. Identification and refinement of statements followed the framework for instrument development of a choice experiment.[56]

Table 3.1. Selected attributes related to preventive therapies tested in the best-worst scaling task

Attributes	Statements
Trust in healthcare providers for infant's health	I trust that doctors and nurses know what is best for infant's health.
Prevention for infant's illness	Medications I take prevent my infant to get infected or become sick.
Side effects on infant	I worry that if I take pills, it can cause side effects on my infant.
Strength	Medications to prevent disease help me feel stronger.
Long life	I can live as long as someone without HIV if I take care of myself.
Interpersonal support for pill take	Friends and families help me to take medications.
Fear of unintended disclosure of HIV status	I worry that taking pills every day tells other people that I have HIV.
Knowledge on pill purpose	I know the purpose of each different medication I take.
Difficulty in daily adherence	I have trouble taking medication on a daily basis.
Travel cost	Getting to the clinic costs me too much money.
Lack of time	I am too busy to come to regular clinic visits.

3.3.4 Experimental design

We used a balanced incomplete block design for this study, which allows for repetition of different combinations of attributes in the subsets of all possible choice scenarios.[68] Each respondent was presented with five statements in each given choice task and asked to choose one statement out of the five that best described her thoughts, as well as the one statement that least described her thoughts. Each of the 11 statements/attributes appeared five times across 11 separate choice tasks (Figure 1). The statements/attributes were presented in an orthogonal array. To reduce burden, each BWS task was presented individually on a flashcard to participants. In addition to BWS tasks, we collected socio-demographics and brief clinical history from each participant.

Now I'm going to show you some sets of 5 statements. For each set, choose the one that BEST describes your thought (or the statement you agree with the most), and the one that WORST describes your thought (the statement you disagree with the most). Each new set will have some different statements, and some will be repeated.

	Best	Worst
A. Friends and families help me to take medications.	□	□
B. I worry that taking pills every day tells other people that I have HIV.	□	□
C. Medications I take prevent my infant to get infected or become sick.	□	□
D. Getting to the clinic costs me too much money.	□	□
E. I trust that doctors and nurses know what is best for infant's health.	□	□

Figure 3.1. Example of a best-worst scaling choice task with five attributes related to preventive therapies among HIV-positive pregnant women

3.3.5 Data analysis

The dependent variable was the participants' choice of best and worst statement in each subset of statements presented to them.[69] The frequency of being chosen as best and as worst over all of the choice tasks was calculated, resulting in a relative BWS score.[70] Each statement chosen as best received a score of 2 while the statement chosen as worst received a score of 0 and all other non-selected statements a score of 1. The aggregate BWS score was calculated as the mean score across all respondents, rescaled from 0 to 100. We compared BW scores by each woman's IPT initiation status at the time of enrollment (on IPT at enrollment vs. not). We used Spearman's rho to compare the ranked correlation of the 11 attributes between the two groups.

Previous studies have shown that a simple BWS score has good validity compared to more sophisticated regression-based methods and good discrimination compared to rating or ranking scales.[45] We ran conditional logistic regressions and compared the results to BWS scores. The coefficients from conditional logistic regressions were compared using Wald

tests, assuming a null hypothesis of no statistically significant difference by IPT initiation status. We also calculated individual BW scores for each statement as above in the scale of 0 to 2. Since each statement appeared five times per respondent, the scores for each statement ranged from 0 (always selected as worst) to 10 (always selected as best) in each individual. The potential association between IPT initiation status and individual BWS scores was examined using multivariable linear regression. Initially, multivariable models contained all potentially important variables with p-value < 0.20. Then final multivariable models were fitted, including only significant individual covariates with p-value < 0.05. All analyses were conducted in STATA 13.

3.4 Results

3.4.1 Baseline patient characteristics

A total of 204 pregnant women with HIV were enrolled and completed the questionnaire (Table 2). Of these, 31% (n=64) were receiving IPT at time of enrollment. At the date of the interview, the mean CD4 count was 469 (±231), and 98% (n=197) were on ART. The mean age was 27(±6) years. The mean gestational age at enrollment was significantly higher in the IPT group (27±1 weeks) than the no IPT group (24±1 weeks, p=0.02). The average time since initial HIV diagnosis was 83±7 days in the IPT group, compared to 44±3 days in the no IPT group (p<0.001).

In the IPT group, 70% (n=45) reported their perceived risk of contracting TB within next year as not at all likely while 89% (n=123) in the no IPT group did so (p<0.001). The proportion of the study population who was unemployed was high (80%) and did not differ by IPT status (p=0.61). About 80% (n=161) of the participants had disclosed their HIV status to partners; this percentage did not differ by IPT status (p=0.28).

Table 3.2. Baseline characteristics by the current status of Isoniazid Preventive Therapy (IPT) among 204 HIV-positive pregnant women, South Africa*

N (%)	**On IPT at enrollment (N=64)**	**No IPT (N=140)**	**p-value†**
Age (years), Mean (± SD)	26.9 (±6.5)	27.3 (±5.5)	0.63
Gestational week at first ANC visit, Mean (± SD)	17.9 (±6.4)	18.1 (± 8.2)	0.91
Gestational week at enrollment, Mean (± SD)	27.0 (±8.0)	23.5 (±8.8)	**0.01**
Time since HIV diagnosis (days), Mean (± SD)	72.5 (±70.9)	43.6 (±41.0)	**<0.001**
CD4 cell count (cells/mm^3), Mean (± SD)‡	490 (±208)	463 (±239)	0.52
Perceived risk of developing TB within next year§			
Slightly likely	19 (29.7)	16 (11.5)	<0.001
It is not at all likely	45 (70.3)	123 (88.5)	
Education			
≤ 9 grade	36 (56.2)	69 (49.3)	0.36
> 9 grade	28 (43.8)	71 (50.7)	
Employment status			
Full time	6 (9.4)	18 (12.9)	0.75
Part time or piece jobs	5 (7.8)	12 (8.6)	
Unemployed	53 (82.8)	110 (78.6)	
Mode of transportation to clinic			
On foot	35 (54.7)	77 (55.4)	0.98
Public taxi or bus	27 (42.2)	57 (41.0)	
Private car or motorbike	2 (3.1)	5 (3.6)	
Transportation cost (Rand)			
Median (IQR)	0 (0, 20)	0 (0, 16)	0.17
Marital status			
Married	8 (12.9)	14 (10.1)	0.09
Living with partner	22 (35.5)	51 (36.7)	
Not living with partner	26 (41.9)	71 (51.1)	
No current partner	6 (9.7)	3 (2.2)	
Disclosure of HIV status to partner			
Yes	50 (84.8)	111 (81.6)	0.60
No	9 (15.3)	25 (18.4)	

*Pearson χ^2 test (discrete variables), t-test (mean comparison for continuous variables) and Mann-Whitney test (median comparison for continuous variables) were used.
†N for on IPT at enrolment and no IPT groups is 48 and 104, respectively.
‡Some variables have missing data.
§No one chose other categories of *moderately likely, very likely or extremely*

3.4.2 Attribute prioritization

Among all participants, trust in healthcare providers for infant's health was prioritized most highly (*BWS score=73.7, SE=1.8*), followed by having a long life *(BWS=67.4±1.9)* and gaining strength through medications (*BWS=61.4±1.6*). Fear of unintended disclosure of HIV status was prioritized the least (*BWS=28.2±1.8*), followed by medication causing side effects in infants (*BWS=33.9±1.8*). Lack of interpersonal support for taking medications *(BWS=42.0±2.0)*, travel cost *(BWS=39.6±1.5)*, and lack of time *(BWS=39.2±1.6)* had lower BW scores as well.

When stratified by IPT status, the overall ranking of the attributes was highly correlated between the two groups, suggesting the relative (ordinal) importance attached to these attributes was strongly correlated (spearman's rho=0.90). Those who were currently on IPT had a significantly lower BWS score for trust in healthcare providers (*BWS=69.3±1.8 vs. 75.6±1.7, p<0.001)* as well as preventive benefits of medications for infant's health (*BWS=56.8±1.9 vs. 62.3±1.8, p=0.002)* and knowledge of purpose of different medication (*BWS=57.3±1.5)* compared to those who were not on IPT. Those receiving IPT also had significantly higher BW scores for receiving interpersonal support for taking medications (*BWS=49.2±1.9)* compared to those who were not on IPT (*BWS=38.8±2.0, p<0.001).* The rankings from conditional logistic regressions by IPT status were the same as those by BWS scores (Supplementary Figure 1).

In the analyses of the association between individual BWS scores and IPT status, this association for interpersonal support persisted, after adjusting for disclosure of HIV status to a partner, gestational weeks and number of adults living in the household (p<0.001). IPT

status was also associated with a higher individual BWS score for travel cost *(0.53±0.20)* after adjusting for transportation costs and disclosure of HIV status to a partner.

Table 3.3. Ranking of 11 statements related to preventive therapies: overall sample and stratified by IPT initiation status during pregnancy

	Overall		Receiving IPT		No IPT	
Statement	BWS	SE	BWS	SE	BWS	SE
I trust that doctors and nurses know what is best for infant's health.	73.7	0.9	69.1	0.9	75.8	0.9
I can live as long as someone without HIV if I take care of myself.	67.5	0.9	65.2	1.0	68.5	0.9
Medications to prevent disease help me feel stronger.	61.3	0.8	61.4	0.9	61.3	0.8
Medications I take prevent my infant to get infected or become sick.	60.7	0.9	56.9	1.0	62.4	0.9
I know the purpose of each different medication I take.	59.7	0.8	57.2	0.8	60.9	0.8
I have trouble taking medication on a daily basis.	44.2	0.8	43.7	0.9	44.4	0.8
Friends and families help me to take medications.	42.0	1.0	49.2	1.0	38.7	1.0
Getting to the clinic costs me too much money.	39.5	0.7	43.1	0.7	37.9	0.7
I am too busy to come to regular clinic visits.	39.3	0.8	36.7	0.9	40.4	0.8
I worry that if I take pills it can cause side effects on my infant.	34.0	0.9	37.7	1.0	32.3	0.9
I worry that taking pills every day tells other people that I have HIV.	28.3	0.9	30.3	0.9	27.4	0.9

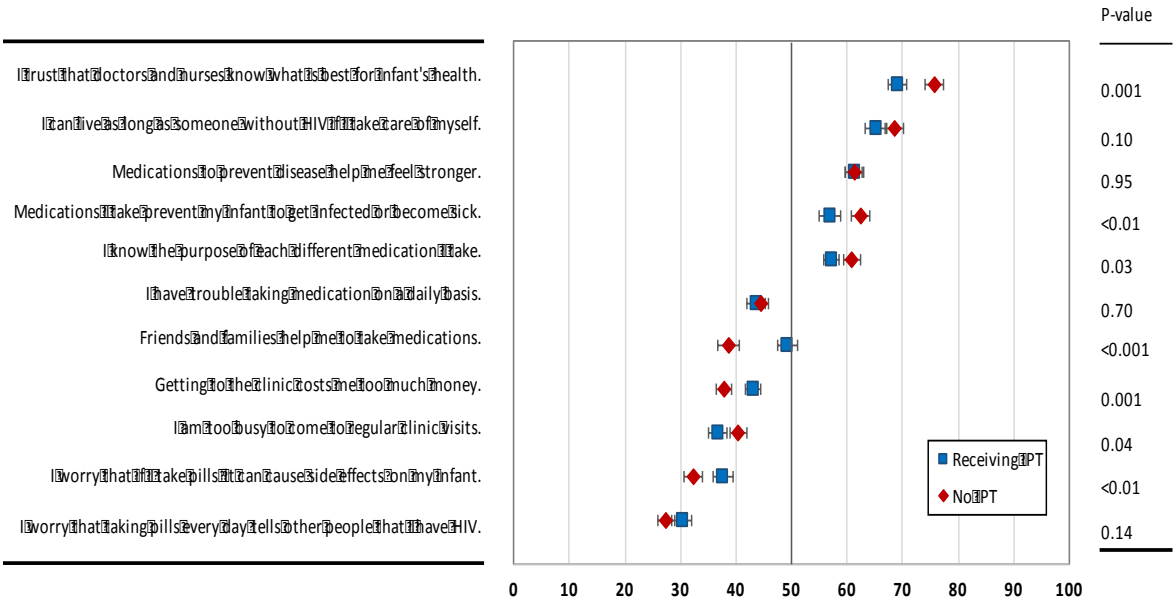

Figure 2. Best-Worst Scaling (BWS) scores for 11 statements related to preventive therapies among HIV-positive pregnant women by IPT status. Blue squares represent the mean priority score among women receiving IPT at enrollment, while red diamonds represent the responses of women not taking IPT. Error bars show 95% confidence intervals, and p-values from Wald tests

3.5 Discussion

Our study findings suggest that pregnant women with a recent HIV diagnosis place a higher prioritization on trust with healthcare providers and medication benefits, compared to transportation costs or lack of time, when these factors were considered simultaneously. BWS methodology has several advantages compared to simple prioritization techniques as it reduces cognitive burden and generates more consistent results by allowing only extreme choices, rather than ranking or rating all potential options.[52] This study of HIV-positive pregnant women's priorities surrounding preventive therapy provides important insight into the patient-centered delivery of such therapies in sub-Saharan Africa.

These findings are supported by reports from other qualitative studies showing that the perceived patient-derived barriers such as lack of money for transport to clinic or pill burden are minor[16] and when health care providers gave sufficient information about regimens, patients had good level of adherence to IPT.[71] Some programmatic interventions have evaluated the impact of providing directly observed therapy for IPT or use of lay health care workers to support self-supervision on treatment adherence, but such interventions resulted in suboptimal completion rates of IPT.[72,73] However, patient education and counseling increased adherence to TB treatment and IPT by empowering patients, although potential effects from these interventions could be dependent on social context and the underlying reasons for poor adherence.[6,73,74] Our study findings suggest that interventions to enhance patients' knowledge could potentially enhance the uptake of and adherence to preventive therapies.

It may seem contradictory that burden of transportation cost, lack of time or stigma from taking daily medications were least prioritized in this study, compared to other studies where these were identified as major barriers for uptake of ART and IPT.[16,22,75] At least three considerations may factor into this counterintuitive result. First, half of the participants in our study walked to clinic; thus, the cost of transportation was often low or nonexistent. Second, recommended clinic visits for pregnant women are aligned with monthly ART pick-up in South Africa, such that any additional transport cost, inconvenience, and stigma related to preventive therapy may have been small. Third, women may not be concerned with pill burden because nearly all (98%) of our study population were receiving their antiretroviral therapy as fixed dose combination tablets, meaning one pill per day.

Although we noted some differences in prioritization between women receiving or not receiving IPT at enrollment, those differences were relatively minor. Ultimately, the overall ranking of statements was similar by IPT status. It is important to note that some of the observed differences by IPT status may reflect differences in the corresponding populations; for example, those not on IPT reported significantly shorter time since HIV diagnosis. Ultimately, our findings suggest that pregnant women's prioritization of statements regarding preventive therapy does not differ according to their previous experience in taking IPT.

There are several limitations in this study. First, we asked participants to choose between statements with both positive and negative connotations in the same choice task. Therefore, our results can only infer which statements were perceived as best, and which were perceived as worst. Future efforts could expand on this work by elucidating the degree to which positive statements refer to facilitators of preventive therapy, and negative statements refer to barriers. Second, recruitment of participants was logistically difficult. Based on the DHIS data in South Africa, we estimate about 40% of eligible women could not be recruited for this study, despite vigorous efforts to enroll all eligible women. We used three interviewers to rotate through all14 clinics for recruitment, which limited our capacity to enroll all eligible women presenting at ANC visits. Third, our methods assume that the importance assigned to the best or worst statement is similar across individuals. We are therefore unable to assess whether specific individuals might prioritize a particular statement much higher, or much lower, than others. Approaches such as scale-adjusted latent class or segmentation may be more appropriate to explore potential heterogeneity in priorities across individuals and develop targeted interventions in future. Finally, we caution that our results comparing priorities by IPT status were not intended to reveal a causal relationship and

should not be interpreted as such. Future studies to elicit preferences in a longitudinal design are warranted.

We have quantified the priorities stated by HIV-positive pregnant women in South Africa across statements related to preventive therapy. We demonstrate that trust in healthcare providers and living a long life are prioritized positively, while fear of HIV disclosure is prioritized the least. These findings illustrate the importance of eliciting and responding to patients' priorities when attempting to implement interventions that seek to prevent future disease, including IPT. Our results can help to design effective patient-centered approaches to IPT delivery among pregnant women with HIV, with the ultimate goal of improving the health of this key population.

Acknowledgments

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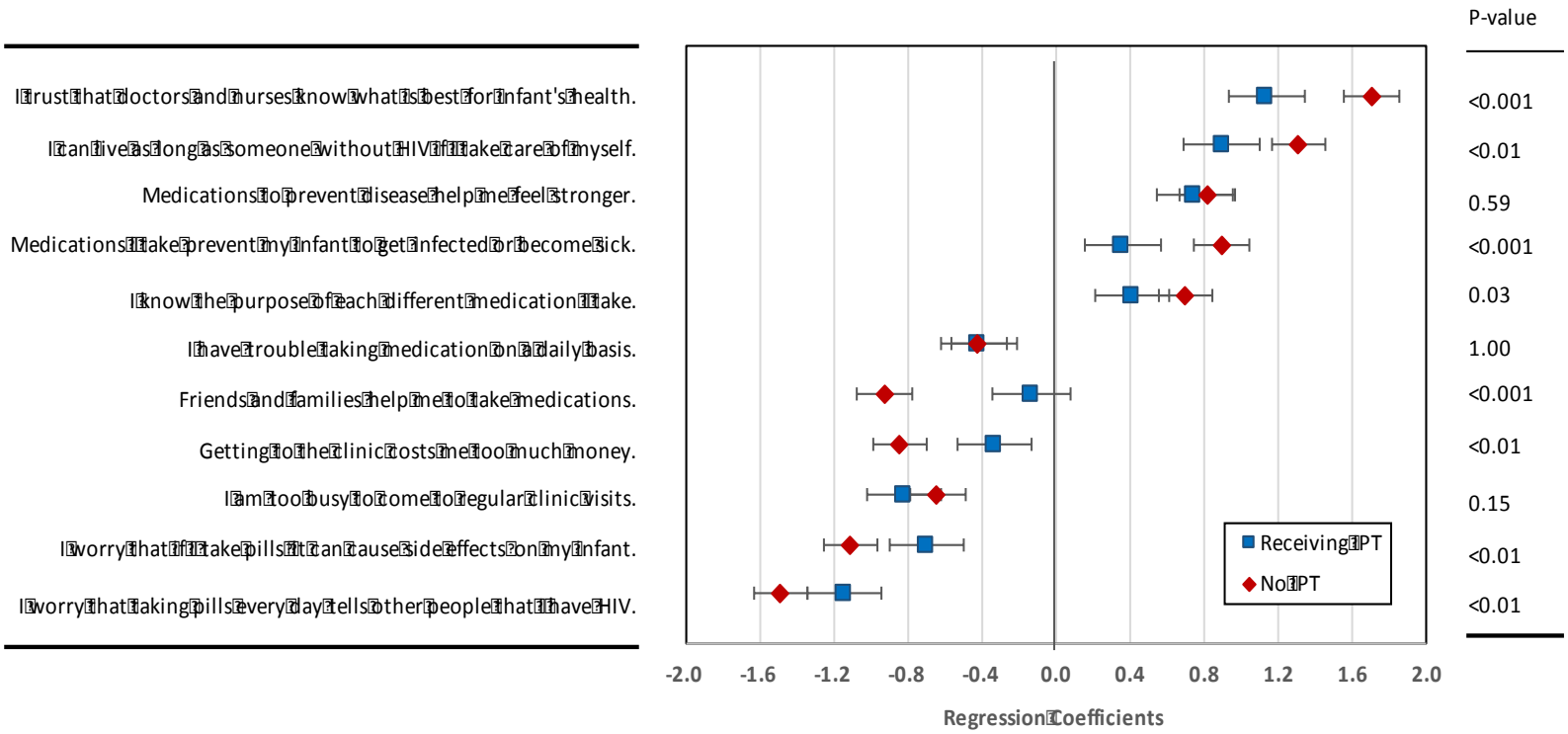
Supplementary Table 3.1. Coefficients and standard errors (SE) from conditional (fixed-effects) logistic regression for 11 statements related to preventive therapies: overall sample and stratified by IPT initiation status during pregnancy

Statement	Overall		Receiving IPT		No IPT		P-value*
	Coefficients	SE	Coefficients	SE	Coefficients	SE	
I trust that doctors and nurses know what is best for infant's health.	1.519	0.057	1.134	0.104	1.703	0.076	<0.001
I can live as long as someone without HIV if I take care of myself.	1.158	0.057	0.897	0.105	1.309	0.075	<0.01
Medications to prevent disease help me feel stronger.	0.775	0.057	0.748	0.103	0.816	0.076	0.59
Medications I take prevent my infant to get infected or become sick.	0.671	0.057	0.358	0.105	0.893	0.076	<0.001
I know the purpose of each different medication I take.	0.598	0.057	0.411	0.104	0.697	0.075	0.03
I have trouble taking medication on a daily basis.	-0.404	0.056	-0.416	0.102	-0.417	0.074	1.00
Friends and families help me to take medications.	-0.602	0.058	-0.135	0.107	-0.923	0.076	<0.001
Getting to the clinic costs me too much money.	-0.655	0.055	-0.336	0.101	-0.843	0.073	<0.01
I am too busy to come to regular clinic visits.	-0.691	0.056	-0.818	0.101	-0.638	0.075	0.15
I worry that if I take pills, it can cause side effects on my infant.	-1.006	0.056	-0.700	0.102	-1.113	0.074	<0.01
I worry that taking pills every day tells other people that I have HIV.	-1.363	0.051	-1.143	0.093	-1.484	0.068	<0.01

*Calculated from Wald tests comparing regression coefficients by IPT status



Supplementary Figure 3.1. Coefficients from conditional logistic regressions for 11 statements related to preventive therapies among HIV-positive pregnant women by IPT status. Blue squares represent the regression coefficients among women receiving IPT at enrollment, while red diamonds represent the regression coefficients among not taking IPT. Error bars show 95% confidence intervals, and p-values from Wald tests comparing regression coefficients by IPT status are presented to the right.

CHAPTER 4

Change in maternal priorities related to preventive therapies for HIV and TB before and after delivery among HIV-positive pregnant women

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4.1 Abstract

Pregnant women newly diagnosed of HIV during pregnancy is often lost to follow up after delivery. We aimed to quantify changes in priorities related to isoniazid preventive therapy (IPT) and antiretroviral therapy (ART) among pregnant women newly diagnosed of HIV in the ante- and postpartum periods. We surveyed pregnant women recently diagnosed with HIV in 14 primary health clinics at enrollment and 14 weeks after delivery in Matlosana, South Africa. Best-worst scaling (BWS) was used to elicit the priorities of 11 attributes related to preventive therapies. Aggregate BWS scores were calculated based on the frequency of participants' selecting each attribute as the best or worst among five options across multiple choice sets. Individual BWS scores were also calculated and rescaled from 0 (always selected as worst) to 10 (always selected as best), and the changes in BWS scores during the ante- vs postpartum periods were compared using a paired t-test. Factors associated with the changes in BWS scores were examined in multiple linear regressions. Spearman's rho was used to compare the ranking of attributes in the ante- vs. postpartum.

Among 204 women surveyed, 154 (75.5%) completed the postpartum visits at the median time of 106 days (IQR 75-190) after delivery. Trust in healthcare providers was most highly prioritized both in the ante- (*individual BWS Score=7.34, SE=0.13)* and postpartum periods (*BWS=7.21±0.11*). Prevention for infants' health was more highly prioritized in the post- *(BWS=6.54±0.09*) vs. antepartum (*BWS=6.11± 0.10*) (p=0.05), which was associated with IPT initiation at enrollment (regression coefficient=0.78 ± 0.33, p=0.001). Difficulty in daily pill-uptake had significantly higher priority in the postpartum (*BWS=5.03±0.11*) than in the antepartum (*BWS=4.43±0.10*) (p<0.01). Overall ranking of attributes was similar at both time periods (spearman's rho=0.90). IPT provision may enhance HIV-positive pregnant women's perceptions for benefits of preventive therapies but interventions to support adherence and build trust in healthcare providers may be needed to increase IPT uptake.

4.2 Introduction

There were 10.4 million new cases and 1.4 million deaths from tuberculosis (TB) globally in 2015.[1] Over 50% of TB cases are co-infected with HIV in South Africa, and TB is the leading cause of mortality among HIV-positive individuals.[76] South Africa has some of the highest rates of HIV and TB among pregnant women whose HIV seroprevalence was about 30% in 2013.[2] TB increases maternal mortality during pregnancy and the postpartum period as well as the risk of mother-to-child HIV transmission and adverse infant outcomes among HIV-positive women.[3,4,35] Thus preventing maternal TB is crucial to ensure the health for both mothers and their infants. Active TB case finding at antenatal care (ANC) clinics in rural South Africa showed that over 20% of HIV-positive pregnant women had at least one symptom of TB at ANC visits.[2]

The national guideline in South Africa recommends that pregnant women diagnosed with HIV are to initiate lifelong antiretroviral therapy (ART) and receive isoniazid preventive therapy (IPT), a daily provision of isoniazid (INH) for up to 36 months to reduce TB incidence and mortality,[20,60] yet many women may not be prepared for these long-term commitment. In sub-Saharan Africa, loss to follow-up (LFU) after delivery among pregnant women diagnosed with HIV can be high as 50%.[8] Adherence rates to ART and IPT also significantly drop after delivery. In a meta-analysis, the proportion of women with adequate adherence for ART (>80%) reduced from 76% during the prenatal period to 53% during postpartum.[17] A recent study in Lesotho showed that 78.5% of HIV-positive pregnant women initiated IPT, and of these, 65% completed their six-month courses.[21]

Several factors are associated with low uptake of IPT among PLWH, such as fear of side effects, non-disclosure of HIV status, and competing socioeconomic responsibilities.[23] Other competing risks including relocation, returning to work, and HIV-related social stigma have been reported as factors for LFU and ART discontinuation in the postpartum period, increasing likelihood of failing viral load suppression.[77–79] Previous qualitative studies among HIV-positive

pregnant women have shown that perceived benefits of ART as "life-giving" as well as treatment support from healthcare workers were important factors.[80,81] Understanding changes in pregnant women's priorities before and after delivery is crucial to deliver services in a most acceptable way to these women. In this study, we sought to quantify the preferences that may encourage or discourage HIV-positive pregnant women's uptake of preventive therapies and engagement in care.

4.3 Methods

4.3.1 Study population and setting

This study was conducted in 14 primary healthcare clinics in Klerksdorp and Potchefstroom, Dr. Kenneth Kaunda District in the North West Province of South Africa. We recruited HIV-positive pregnant women from 14 primary care public health clinics (PHC) in the Dr. Kenneth Kaunda health district in the North West province, South Africa from February 2015 to February 2016. This study was nested within an ongoing cluster randomized trial in the same 14 clinics, which compares proportions with known TB infection status and IPT initiation among newly diagnosed HIV patients in clinics using two different diagnostic tests for latent TB infection.[36,57] Of a total of 24 PHCs from Matlosana and Tlokwe subdistricts, 14 PHC were selected to be included for TEKO substudy to cover a range of patient volumes, urban vs rural setting, geography and clinic hours.

Patients were eligible for enrollment if they were ≥18 years old, newly diagnosed with HIV in the preceding six months, and able to read one of the following languages: English, Xhosa, Setswana or Zulu. We sought to enroll all eligible pregnant patients during the study period, and the percentage of enrollment was calculated based on the number of eligible patients reported in the District Health Information System (DHIS) between January 2015 and July 2015,

when the DHIS data was available.[63] Written informed consents were obtained from all participants. The study was approved by the institutional review boards at the Johns Hopkins School of Medicine and University of Witwatersrand.

4.3.2 Study design

We conducted a longitudinal survey incorporating a best-worst scaling (BWS) instrument (Case 1) from January 2015 to September 2016. All pregnant women were enrolled during pregnancy and completed one follow-up visit at the 14 weeks postpartum. BWS (Case 1) is a stated-preference method which allows for ranking of the relative importance of a list of attributes in a continuous quantitative scale and has been increasingly used in healthcare research to understand patients' perspectives and preferences.[64] Each respondent chooses the best and the worst attribute from a set of available options in a given choice task, assuming that participants choose a best-worst pair maximizing the difference in the underlying utility.[52,56,65,66]

4.3.3 Selection of attributes

We identified attributes likely to influence women's decision-making regarding uptake of preventive therapies through literature review and prior in-depth interviews about patients' experiences and perceptions of ART and IPT, which focused on the participants' general perceptions of healthcare services, their understanding of TB, experience and views on IPT, and barriers and facilitators of medication adherence.[57,22,23,67] Four themes were ascertained: treatment benefits for maternal and infant heath, interpersonal support, trust in healthcare services, and structural barriers. A total of 11 attributes were chosen, including roughly equal numbers of potential barriers and facilitators for initiation of IPT (Table 1). Attributes were converted to simple statements, which were then reviewed and refined by clinical experts and

healthcare providers in the clinics. Identification and refinement of statements followed the framework for instrument development of a choice experiment.[56]

Table 4.1. 11 Selected attributes related to preventive therapies tested in the best-worst scaling task

Attributes	Statements
Trust in healthcare providers for infants' health	I trust that doctors and nurses know what is best for infant's health.
Prevention for infant's illness	Medications I take prevent my infant to get infected or become sick.
Side effects on infant	I worry that if I take pills, it can cause side effects on my infant.
Strength	Medications to prevent disease help me feel stronger.
Long life	I can live as long as someone without HIV if I take care of myself.
Interpersonal support for pill take	Friends and families help me to take medications.
Fear of unintended disclosure of HI status	I worry that taking pills every day tells other people that I have HIV.
Knowledge on pill purpose	I know the purpose of each different medication I take.
Difficulty in daily adherence	I have trouble taking medication on a daily basis.
Travel cost	Getting to the clinic costs me too much money.
Lack of time	I am too busy to come to regular clinic visits.

4.3.4 Experimental design

We used a balanced incomplete block design for this study, which allows for repetition of different combinations of attributes in the subsets of all possible choice scenarios.[68] Each respondent was presented with five statements in each given choice task and asked to choose one statement out of the five that best described her thoughts, as well as the one statement that least described her thoughts. Each of the 11 statements/attributes appeared five times across 11 separate choice tasks (Figure 4.1). The statements/attributes were presented in an orthogonal array. To reduce burden, each BWS task was presented individually on a flashcard to participants.

Now I'm going to show you some sets of 5 statements. For each set, choose the one that BEST describes your thought (or the statement you agree with the most), and the one that WORST describes your thought (the statement you disagree with the most). Each new set will have some different statements, and some will be repeated.

	Best	Worst
A. Friends and families help me to take medications.	□	□
B. I worry that taking pills every day tells other people that I have HIV.	□	□
C. Medications I take prevent my infant to get infected or become sick.	□	□
D. Getting to the clinic costs me too much money.	□	□
E. I trust that doctors and nurses know what is best for infant's health.	□	□

Figure 4.1. Example of a best-worst scaling choice task with five attributes related to preventive therapies among HIV-positive pregnant women

4.3.5 Sociodemographic, clinical variables and adherence measurement

Participants' sociodemographic and clinical information was obtained at enrollment. Details related to delivery and history of breastfeeding were obtained in the postpartum visit. Infant HIV status and clinical information were collected if the HIV polymerase chain reaction (PCR) test results were available. Participants were also asked about the degree of support received from healthcare workers, family or friends to take medications and whether they were satisfied with the support. Self-reported adherence rates were measured by the AIDS Clinical Trials Group (ACTG) Adherence Questionnaire, which is based on 4-day recall with five items. This questionnaire has been extensively used and validated in other studies.[39–42] Being adherent to ART or IPT was defined as taking all drugs in the previous 4 days. Adherence to IPT was also measured by testing eligible participants' urine samples by IsoScreen kit (GFC Diagnostics Limited, Oxfordshire, UK), a test to measure the presence of INH metabolites over the past 24-48 hours. Black/violet color indicates that the patient has taken a INH within 1 day; green color indicates taking it within 2 days; and yellow means no INH taken within 2 days. There is no

routine test for INH or monitoring for IPT at the study sites so IsoScreen kit was performed by trained study interviewers.

4.3.6 Data analysis

The outcome was the participants' choice of best and worst statement in each subset of statements presented to them in the ante- and postpartum.[69] The frequency of best and worst statement choices across all choice tasks was calculated, resulting in a relative BWS score.[70] Each statement chosen as best received a score of 2 while the statement chosen as worst received a score of 0 and all other non-selected statements a score of 1. The aggregate BWS score was calculated as the mean score across all respondents, rescaled from 0 to 100. Previous studies have shown that a simple BWS score has good validity, compared to more sophisticated regression-based methodsand good discrimination compared to rating or ranking scales.[45] Conditional logistic regression models were fitted and compared to BWS scores. The coefficients from conditional logistic regression models were compared using Wald tests under the null hypothesis that there is no statistically significant different in BWS scores in the antepartum vs. postpartum.

We also calculated individual BWS scores for each statement as above in the scale of 0 to 2 in the antepartum and postpartum, separately. Since each statement appeared five times per respondent, the scores for each statement ranged from 0 (always selected as worst) to 10 (always selected as best). The difference in the antepartum vs. the postpartum was calculated and compared using paired t-test. We examined the potential association between individual BWS scores and other factors in multivariable linear regression. Initially, multivariable conditional logistic regression models contained all potentially important variables with p-

value < 0.20. Then final multivariable conditional logistic regression models were fitted, including only significant individual covariates with p-value < 0.05. All analyses were conducted in STATA 13.

4.4 Results

4.4.1 Patient characteristics

Of 204 pregnant women who were enrolled during pregnancy, 47 did not complete the follow-up visits. Of these 27 participants lost to follow up, 20 (42.6%) were relocated to out of the study area, 23 (49.9%) were contacted three times but could not be reached, and 4 lost interest in the study or refused to participate further. The baseline characteristics were similar among those who were lost to follow up and those included in the analysis. Of 155 (75.6%) who had at least one follow-up visit, 77 (49.7%) were followed at 14 week visit, 33 (21.3%) at 6 weeks visit and 45 (29.0%) at later than 14 weeks after delivery. The mean time since delivery at follow-up visits was 15 (IQR: 11-27) weeks.

About thirty percent (n=45) were receiving IPT while 98% (n=151) were on ART at enrollment (Table 4.2). The mean age was 27(±6) years with the mean gestational age at 26(±1) weeks at enrollment. The mean CD4 cell count was 457 (±242) cells/mm^3 with the average time since initial HIV diagnosis of 55±52 days. The unemployment rate was high (>80%). About 80% (n=125) of the participants had disclosed their HIV status to their partners, and 39 participants (19.5%) reported that they planned to stay with family in home resident after delivery.

In the postpartum, of 155 participants, 2 (1.3%) infants were found to be HIV-positive; 125 (89.3%) had negative HIV status and 13 (8.4%) had unknown HIV status. There were 10 (6.5%) participants with incomplete data on infant HIV status. Near 90% (n=132) of participants ever breastfed their infants, and 57% (n=88) was still breastfeeding. 4 (5.4%) reported that they experienced a stock-out problem at the clinic for IPT or ART in the last 12 months. While 49.4% reported that they received somewhat or a lot of support from friends and family to remember taking medications, 88.4% (n=137) did so from healthcare providers ($p<0.001$). About 95% people of patients who were on ART reported that they were informed about side effect and reasons to take ART while 89.3% of people who were on IPT did so.

Of 36 participants who had follow-up visits completed within 12 months since the date of IPT initiation, 9 (25%) were still prescribed to take IPT, and the results of IsoScreen kit are following: 4 black/violet (INH taken within 1 day), 1 green (INH taken within 2 days) and 2 yellow (no INH taken within 2 days). All of these participants reported being adherent to IPT based on self-reported adherence measure. Additionally, 18 were initiated on IPT after study enrollment. Of these, 13 out of 14 (92.8%) were adherent to IPT based on self-reported adherence and matched with IsoScreen results for being adherent (81.8%, n=9). For ART, everyone reported taking ART in the postpartum visits; of 145 who completed the adherence questionnaires, 94.0% (n=140) reported to be adherent to ART.

Table 4.2. Baseline characteristics and follow-up variables by the status of Isoniazid Preventive Therapy (IPT) at enrollment among 154 HIV-positive pregnant women, South Africa*

N (%)	**On IPT at enrollment (N=45)**	**No IPT (N=109)**	**p-value†**
Age (years), Mean (± SD)	27.5 (± 6.4)	27.4 (± 5.6)	0.89
Gestational week at first ANC visit, Mean (± SD)	18.6 (±6.2)	18.1 (±8.2)	0.70
Gestational week at enrollment, Mean (± SD)	27.0 (±7.4)	23.8 (±9.1)	**0.05**
Time since HIV diagnosis (days), Mean (± SD)	77.9 (±67.7)	44.9 (±41.4)	**<0.001**
CD4 cell count (cells/mm^3), Mean (± SD)**	481 (±227)	467 (±248)	0.79
Perceived risk of developing TB within next year*			
Slightly likely	16 (35.6)	12 (11.1)	<0.001
It is not at all likely	29 (64.4)	96 (88.9)	
Education**			
≤ 9 grade	9 (25.0)	21 (26.9)	0.83
> 9 grade	27 (75.0)	57 (73.1)	
Employment status			
Full time	2 (4.4)	11 (10.1)	0.35
Part time or piece jobs	5 (11.1)	7 (6.4)	
Unemployed	38 (84.4)	91 (83.5)	
Mode of transportation to clinic			
On foot	23 (51.1)	61 (56.0)	0.86
Public taxi or bus	21 (46.7)	46 (42.2)	
Private car or motorbike	1 (2.2)	2 (1.8)	
Transportation cost (Rand)			
Median (IQR)	0 (0, 20)	0 (0, 16)	0.14
Marital status			
Married	7 (18.4)	10 (9.3)	0.31
Living with partner	13 (34.2)	39 (36.1)	
Not living with partner	18 (47.4)	59 (54.6)	
Disclosure of HIV status to partner			
Yes	28 (62.2)	54 (50.5)	0.18
No	17 (37.8)	53 (49.5)	

*Pearson χ^2 test (discrete variables), t-test (mean comparison for continuous variables) and Mann-Whitney test (median comparison for continuous variables) were used.
**Some variables have missing data.
***No one chose other categories of *moderately likely, very likely or extremely likely*.

4.4.2 Aggregate BWS scores in the antepartum and postpartum

Trust in healthcare providers was prioritized most highly in the postpartum (*BWS =72.1, SE=2.6*), followed by having a long life (*BWS=68.6±2.5*), and they did not significantly differ from the antepartum (Table 4.3). Prevention of infants' illness had significantly higher scores in the postpartum (*BWS=65.4±2.4)* than in the antepartum (*BWS=61.1±2.2*) (*p<0.01)*. Difficulty in daily medication adherence was also significantly more prioritized in the postpartum (*BWS=50.3± 1.8)* than in the antepartum *(BWS=44.3±1.6) (p<0.001).* Travel cost (*p<0.01)* and side effects for infants (*BWS=28.4±1.0 vs. 33.6±1*) (*p<0.001)* were less prioritized in the postpartum than in the antepartum.

Table 4.3. Frequency of attributes chosen among 11 statements and aggregate BWS scores in the antepartum vs. postpartum (N=154)

11 Statements	Antepartum				Postpartum				p-value
	Best*	Worst**	BWS score	SE	Best	Worst	BWS score	SE	
I trust that doctors and nurses know what is best for infant's health.	387	27	73.4	2.6	361	20	72.1	2.6	0.38
I can live as long as someone without HIV if I take care of myself.	324	51	67.7	2.4	306	19	68.6	2.5	0.53
Medications I take prevent my infant to get infected or become sick.	241	70	61.1	2.2	265	28	65.4	2.4	<0.01
Medications to prevent disease help me feel stronger.	213	45	60.9	2.2	148	20	58.3	2.1	0.04
I know the purpose of each different medication I take.	201	34	60.8	2.2	227	19	63.5	2.3	0.04
I have trouble taking medication on a daily basis.	70	157	44.3	1.6	104	100	50.3	1.8	<0.001
Friends and families help me to take medications.	117	243	41.7	1.5	98	266	38.9	1.4	0.1
I am too busy to come to regular clinic visits.	45	197	40.1	1.4	69	154	44.5	1.6	<0.01
Getting to the clinic costs me too much money.	25	195	39.0	1.4	16	244	35.2	1.3	<0.01
I worry that if I take pills it can cause side effects on my infant.	38	290	33.6	1.2	18	350	28.4	1.0	<0.001
I worry that taking pills every day tells other people that I have HIV.	27	376	27.3	1.0	43	435	24.5	0.9	0.06

*Number of times chosen as best attribute in a given choice set is calculated. A total of 770 (154 respondents x 5 times per attribute) was available to be selected per attribute.

**Number of times chosen as worst attribute in a given choice set is calculated.

4.4.3 Changes in individual BWS scores in the antepartum vs. postpartum

When individual BWS scores were compared in the antepartum vs. postpartum, we observed similar patterns of prioritization (Table 4.4). Trust in healthcare providers for infants' health was prioritized most highly both in the ante- (*BWS=7.2, SE=0.1*) and the postpartum (*BWS=7.3±0.1*), and these did not significantly differ (p=0.46) (Figure 4.2). Having a long life was similarly prioritized in the ante- (*BWS=6.8±0.1*) and postpartum (*BWS=6.9±0.1*) (p=0.56). Compared to the antepartum, prevention for infants' health was slightly more prioritized in the postpartum (p=0.05) as well as difficulty in daily pill-take (p<0.01) and lack of time to come to regular clinic visits (p=0.01). Fear of unintended disclosure of HIV status was least prioritized in both antepartum vs. postpartum (*BWS=2.7±0.1* vs. *2.5±0.2*, p=0.19), followed by medication causing side effects in infants (*BWS=3.4±0.1* vs. *2.8±0.1*, p<0.01).

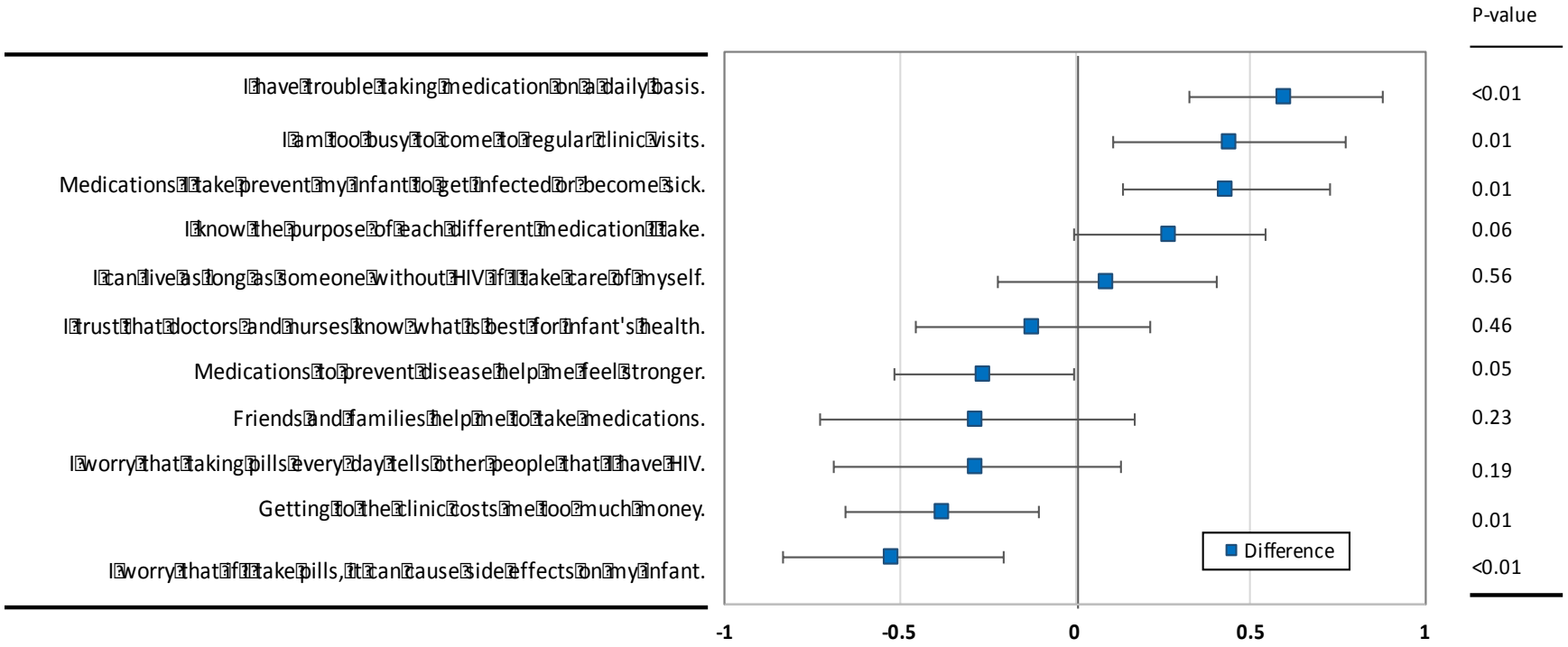

Figure 4.2. Changes in individual Best-Worst Scaling (BWS) scores for 11 statements related to preventive therapies among HIV-positive pregnant women in the postpartum vs. antepartum periods. Error bars show 95% confidence intervals, and p-values from Wald tests comparing mean BWS scores by timing of visits are presented to the right.

Table 4.4. Individual Best-Worst Scaling scores for 11 statements in the antepartum vs. postpartum periods among 154 HIV-positive pregnant women

Statement	Antepartum		Postpartum		Difference		
	Mean	SE	Mean	SE	Mean	SE	p-value*
I trust that doctors and nurses know what is best for infant's health.	7.34	0.13	7.21	0.11	0.12	0.17	0.46
I can live as long as someone without HIV if I take care of myself.	6.77	0.13	6.86	0.1	-0.09	0.16	0.56
Medications I take prevent my infant to get infected or become sick.	6.11	0.12	6.54	0.09	-0.43	0.15	0.01
Medications to prevent disease help me feel stronger.	6.09	0.1	5.83	0.07	0.26	0.13	0.05
I know the purpose of each different medication I take.	6.08	0.11	6.35	0.1	-0.27	0.14	0.06
I have trouble taking medication on a daily basis.	4.43	0.1	5.03	0.11	-0.59	0.14	**<0.01**
Friends and families help me to take medications.	4.17	0.17	3.89	0.17	0.27	0.23	0.23
I am too busy to come to regular clinic visits.	4.01	0.12	4.45	0.14	-0.44	0.17	**0.01**
Getting to the clinic costs me too much money.	3.9	0.11	3.52	0.09	0.38	0.14	**0.01**
I worry that if I take pills it can cause side effects on my infant.	3.36	0.12	2.84	0.1	0.52	0.16	**<0.01**
I worry that taking pills every day tells other people that I have HIV.	2.73	0.14	2.45	0.18	0.28	0.21	0.19

*P-values were calculated from Wald tests comparing mean BWS scores by timing of visits.

4.4.4 Association between changes in individual BWS scores and other factors

Several factors were examined for the association with changes in the individual BWS scores in the antepartum vs. postpartum using multiple regression. Being married was significantly associated with a higher individual BWS score for difficulty in daily pill-take in the postpartum (coefficient (ß)=0.72±0.28, p=0.01). Lack of time to come to regular clinic visits was associated with the decrease in the individual BWS scores in the postpartum (ß=-0.82±0.35, p=0.02).

IPT initiation at enrollment was associated with significantly higher individual BWS scores for prevention for infants' health (ß=1.09±0.32, p=0.001) after adjusting for TB treatment history and number of previous pregnancy. It was also associated with decrease in the BWS scores for side effects on infants (ß=-0.87±0.35, p=0.02) and interpersonal support from families and friends (ß=-1.61±0.50, p=0.001). Being adherent to ART was significantly associated with higher BWS score for living a long life (ß=1.71±0.65, p=0.01).

4.5 Discussion

Pregnant women newly diagnosed with HIV antepartum face the decision of starting lifelong ART, and this decision is often prioritized around infants' health. Our study findings suggest that pregnant women with a recent HIV diagnosis receiving ART highly prioritize trust with healthcare providers and prevention of infants' illness, and these preferences persist after delivery. In the postpartum, women consistently showed high prioritization on having a long life and perceived medication benefit for their own health, and barriers such as lack of time or high transportation cost to come to regular clinic visits were less prioritized. Interestingly, those who had initiated IPT during pregnancy were more likely to perceive the

benefits of medications on infant's health in the postpartum period. This may be supported that almost everyone (96.4%) who received IPT reported that clinical staffs told them the purpose of IPT during the last clinic visit. The statement of knowing the purpose of different medications was also highly perceived, suggesting that women in the postpartum are aware of the benefits of ART and IPT for both their own and infants' health. Lack of time to come to regular clinic visits was more prioritized in the postpartum period, potentially reflecting the impact of life-changing event of having a newborn baby.

Earlier studies documented that HIV-positive women are less likely retained in care and adherence rates to ART drop in the postpartum. [7,8,17] Mothers could be less motivated to take preventive therapies and seek HIV cares once they had protected their infants from HIV transmission and successfully weaned them.[82] Other reasons were reported as feeling well, demands of everyday life or HIV-related stigma. [7,8,17] In this study, even in the postpartum period and after weaning, mothers highly prioritized medication benefits for their own health.

In our study, most participants were taking one pill of fixed-dose combination (FDC) and one daily isoniazid pill under IPT. The self-reported adherence to ART was very high as > 90% although more objective measurement like viral suppression was not available and the high self-reported adherence rate could have been overstated.[82,83] IPT prescription at enrollment was low at around 30%, and the duration of IPT prescription could not be obtained from patients' medical charts for most of participants. Of those who were receiving IPT at enrollment and in the postpartum, the proportion of people adhering to IPT was sub-optimal based on the results of IsoScreen kit although our sample size may be too small to detect any significant difference in level of adherence to IPT. More participants reported that they had trouble taking medication on a daily basis in the postpartum. Counseling and

interventions to address challenges related to adherence may enhance IPT uptake in the postpartum.

Our study has some contradictory finding to previous studies. Previous study showed that patients may be concerned about the side effects of IPT and be less likely to complete the treatment.[84] We found that mothers were consistently least concerned about side effects that the treatment may impact on infants; rather, benefits of preventive therapies for both infants and maternal health were highly prioritized over side effects.

Trust in healthcare providers was highly perceived. About 90% of study participants reported that they received help from clinical staff to remember taking medications. Other studies have shown that patients could have good adherence to IPT and retention in care if they were informed about the benefits of the drugs, [71] and patient education and counseling increased adherence to TB treatment and IPT by empowering patients.[6,73,74] Contrary to the high proportion of participants receiving support from clinical staff, half of participants reported that they received little or no support from friends and family to remember taking medications in the postpartum. In the qualitative interviews conducted in the same 14 study clinics in South Africa, family was mentioned as a common and importance source of support.[57] Having a supportive system is vital for retention in care and adherence to ART and IPT among HIV-positive individuals,[67] especially among postpartum women.[85] The follow-up period of this study was relatively short and the sample size was quite small thus we could not ascertain the impact of lack of support from family and friends on the long term health outcomes. More comprehensive package of care would be needed to inform and engage family members in this setting.

This is one of the first studies to use a choice experiment in understanding maternal priorities to preventive therapies around the time of delivery among HIV-positive pregnant women. We demonstrated that a choice experiment such as BWS can be used as an alternative to quantitative rating or ranking scales. BWS experiment has a particular strength to discriminate among attributes.[45] It also allows to compare attributes from different domains from individual to interpersonal and community levels thus provides quantitative measure for utilities to be gained with targeted interventions to improve attributes. This study is also meaningful to elicit changes in priorities using a same set of questions in a longitudinal design.

There are several limitations in this study. First, recruitment of participants was challenging and there was a high loss to follow-up; of these, 50% of LFU were due to relocation to outside of study areas. The baseline characteristics did not differ between those who were lost to follow up vs. retained in the study; however, we cannot determine whether these women may have different priorities regarding health or structural barriers to linkage to care. We tracked down mothers who missed regular clinic visits at 14 weeks and tried to capture them in the postpartum. Second, we could not verify the validity of self-reported adherence against other methods, such as pill counts or viral suppression data. Third, we asked participants to choose between statements with both positive and negative connotations in the same choice task. Therefore, our results can only infer which statements were perceived as best, and which were perceived as worst. However, we saw that the absolute rankings of preferences remained similar in the postpartum, supporting that our instrument likely had good face validity. The directionality of changes in the priorities across attributes was supported by other literatures as well.

4.6 Conclusion

In summary, we have quantified maternal priorities for preventive therapies among HIV-positive pregnant women around the time of delivery. We demonstrate that trust in healthcare providers and medication benefits for infants and their own health are most highly prioritized in the antepartum and consistently in the postpartum. However women may have more difficulty in adhering to therapies and coming to regular clinic visits in the postpartum. These study findings provide important insight to design patient-centered intervention and program for IPT delivery with the ultimate goal of improving the health of HIV-positive mother s and their infant in high HIV and TB burden settings.

CHAPTER 5

Changing views of health promotion among HIV-positive pregnant women in South Africa before and after delivery: A choice experiment

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5.1 Abstract

HIV-positive pregnant women who are initiated on life-long therapy have a high risk of becoming lost to follow-up (LFU) after delivery. We examined maternal motivation to take preventive therapies before and after delivery among pregnant women newly diagnosed with HIV. We enrolled pregnant women (≥18 years) with a recent HIV diagnosis (<6 months) at 14 public primary health clinics in Matlosana, South Africa and followed them at 14 weeks postpartum. The motivation for taking preventive therapies was estimated using a conjoint analysis, with each respondent randomly receiving eight tasks comparing seven possible health benefits identified through literature reviews and key informant interviews. Data was analyzed using conditional logit and mixed logit (MXL) models in the antepartum vs. postpartum. Coefficients are reported with 95% confidence intervals and standard errors.

Sixty-five women completed surveys at both enrollment and 14 weeks postpartum. All women were already started on ART while 21 (32%) were receiving IPT at enrollment. The mean CD4 count was 436 (± 246) cells/mm^3. In the antepartum, preventing HIV transmission to partners (coefficients (ß)=0.87, 95% CI: 0.64-1.11), followed by keeping them healthy for family (ß =0.75, 95% CI: 0.52-0.97), was the most prioritized motivator in conditional logistic regression. Such prioritization significantly decreased in the postpartum ($p<0.001$). While keeping high CD4 count was least prioritized in the antepartum (ß=0.19, 95% CI: -0.04, 0.43), it was most prioritized in the postpartum (ß=0.39, 95% CI 0.21-0.57). The results were similar in MXL models. We demonstrate that social motivation such as supporting family and preventing HIV transmission to partners may pose greater motivation for taking preventive therapies in the antepartum while individual health benefits are more prioritized in the postpartum. Changes in motivators need to be incorporated to deliver targeted health promotion messages among HIV-positive women around the time of delivery.

5.2 Introduction

It is estimated that about one-third of the 33 million HIV-positive individuals are co-infected with Mycobacterium tuberculosis (TB) worldwide.[86] Women at reproductive age have a higher HIV prevalence and are at the greatest risk of converting latent TB infection to active TB disease compared to men at similar age in sub-Saharan Africa.[9,87] Pregnancy is an important gateway to the health system to provide routine screening tests including HIV and TB. It is during antenatal care (ANC) visits that many women first learn that they are infected with HIV. In South Africa, about 37% of women who attended ANC visits were HIV-positive and of these 23% reported any symptom of TB in 2011.[12] The prevalence of TB in HIV-positive pregnant women is similar to that of the general population as 795/100,000 but they might be at 10-fold increased risk of active TB compared to HIV-uninfected pregnant women.[88]

The national guidelines for preventing mother-to-child transmission (PMTCT) and TB recommend that all pregnant and breastfeeding HIV-positive women are initiated on life-long antiretroviral therapy (ART) regardless of CD4 cell counts and if infected with TB, isoniazid preventive therapy (IPT) up to 36 months. ART not only prevents vertical HIV transmission but also achieves better long-term maternal health outcomes, and IPT can reduce the risk of developing TB among people living with HIV (PLWH) up to 60%.[20,60,89] Nevertheless, implementation of these guidelines remain challenging. Many women may not be prepared for this long-term treatment commitment and fallen out of care after delivery. A recent study showed that up to half of women who initiated ART during pregnancy were lost to follow up six months after delivery in South Africa.[8,7] Adherence rates to ART and IPT also significantly drop in the postpartum.[18,90] In a meta-analysis done among sub-Sharan African studies, the proportion of women with adequate adherence for ART (>80%) reduced from 76% in the antepartum to 53%

during the postpartum period.[17] Another study in Lesotho showed that 78.5% of HIV-positive women initiated IPT but 65% of these women completed the 6 month IPT.[21]

Several factors have been associated with high loss to follow-up and lower adherence in postpartum period including late presence at ANC services, low social support, relocation during pregnancy, or lack of counseling and education.[91–93] Among HIV-positive individuals, perceived benefits of ART as "life-giving" as well as treatment support from healthcare workers have been reported as important factors to adhere to ART.[80,81] However, many pregnant women are often at an earlier stage of HIV disease without clinical symptoms but are initiated on ART during pregnancy to prevent HIV transmission to infants. Once they protect their babies from infection and stop breastfeeding, they are less likely motivated to remain in care.[82] These factors emphasize the importance of understanding what motivates HIV-positive pregnant women to take ART and IPT around the time of delivery in order to provide targeted interventions thus to ensure better adherence and retention in care in long-term. In this study, we sought to quantitatively measure the relative importance of potential maternal motivators to take preventive therapies among pregnant women newly diagnosed of HIV using a conjoint analysis.

5.3 Methods

5.3.1 Study participants

This study was conducted from 14 primary care public health clinics in the Dr. Kenneth Kaunda health district in the North West province, South Africa from November 2014 to December 2015. It was nested within an ongoing cluster randomized trial in the same 14 clinics, which compares proportions with known TB infection status and IPT initiation among newly diagnosed HIV patients in clinics using two different diagnostic tests for latent TB infection.[36,57]

Clinics were chosen to cover a range of patient volumes, urban vs rural setting, geography and clinic hours. Patients were eligible for enrollment if they were ≥18 years old, newly diagnosed with HIV in the preceding six months, and able to read either English, Xhosa, Setswana or Zulu. We sought to enroll all eligible patients during the study period. The study was approved by the institutional review boards at the Johns Hopkins School of Medicine and University of Witwatersrand.

5.3.2 Study design

We conducted a longitudinal survey using a conjoint analysis to elicit pregnant mothers' motivation to take preventive therapies. Conjoint analysis refers to methods that elicit respondents' preferences by allowing them to make choices over sets of hypothetical alternatives, where each alternative is described by several characteristics (i.e. attributes) related to health services or goods of interest.[24,48] It has been applied to measuring preferences for a wide range of health applications including HIV prevention [94,95] and delivery services among women in rural settings.[96] The advantage of conjoint analysis is that it allows to quantity the degree of preferences (i.e. preference weights) associated with different attributes.

Through key informant interviews, literature review and expert consultations, we determined seven possible benefits of preventive therapies that may matter most to patients. The seven possible benefits of preventive therapies included (1) Keeps me healthy for my family (2) Keeps me from giving HIV to my partner (3) Keeps my HIV disease under control (4) Keeps me health from my family (5) Prevents me from getting sick from infections (6) Keeps me healthy and working (7) Prevents me from getting TB (Table 5.1). All conjoint tasks were forced choices (i.e. respondent could not opt out or choose neither option). An example of conjoint tasks is shown in Figure 5.1. In addition to completing the tasks, individuals were also asked to provide age, gender, ethnicity and other sociodemographic variables.

Table 5.1. List of seven potential motivations for taking preventive therapies

Label	Motivator
Preventing HIV transmission	Keeps me from giving HIV to my partner
Overall health	Keeps me healthy and working
Supporting family	Keeps me healthy for my family
High CD4 counts	Keeps my CD4 high
Disease control	Keeps my HIV disease under control
Preventing infections	Prevents me from getting sick from infections
Preventing TB	Prevents me from getting TB

We used a fractional factorial design where seven possible benefits were randomly allocated across eight questions per respondent.[59] Each benefit was mutually exclusively presented in one of two options in an orthogonal array design. We used a main-effects orthogonal array, assuming that there are no interactions between these seven possible benefits.[59,97] To reduce cognitive burden, each question was presented in a flashcard separately. Each respondent was asked same questions both at enrollment and postpartum visits.

We asked some people with HIV to describe the reasons why they drink medications to prevent disease. In each question, I will show you what two people said, and ask you which person's statements BEST describe the way YOU think about why to take preventive medications.	
Person 1: **Keeps my CD4 high** **Keeps my HIV disease under control** **Keeps me healthy for my family** **Prevents me from getting TB** □ I am more like this person	**Person 2:** **Keeps me healthy and working** **Prevents me from getting sick from infections** **Keeps me from giving HIV to my partner** □ I am more like this person

Figure 5.1. Example of a conjoint analysis task with seven motivations related to preventive therapies among

5.3.3 Statistical analysis

The data was analyzed using conditional logit and mixed logit models with fitting all motivators as explanatory variables to estimate relative utility or preference weight of each motivator in the antepartum and postpartum periods.[26,98,55] Conditional logit model assumes that individuals have same underlying preferences and the random errors associated with choices are independent and identically distributed while mixed logit model assumes that individuals' preferences may vary and can be described as continuous distribution. Mixed logit model also allows to control for intra-individual correlations due to repeated responses. Coefficients from both models can be interpreted as preference or utility weights associated with that attribute.[55]

The primary outcome in the analysis was the choice between two sets of motivators in a given choice task. The independent variables were a set of seven dichotomous variables where each motivator presented on the right side was coded as one and the motivator not presented on the right ride was coded as zero. This coding scheme was applied since all seven benefits needed to be mutually exclusively presented in either side of choice sets. We fitted additional models with interaction terms between each motivator and being postpartum visits to explore whether participants had different priorities at enrollment and postpartum visits. Wald tests were used to test the statistical significance of the interaction terms. Coefficients are presented with standard errors and 95% confidence intervals. All analysis was performed in STATA 13.0.

5.4 Results

5.4.1 Participant characteristics

A total of 72 people newly diagnosed with HIV were enrolled and completed the questionnaire. 65 women completed surveys at both baseline and follow-up visit (Table 5.2). At baseline, the mean age was 27 years (IQR:22-31 years) with average time since initial HIV

diagnosis of 51±75 days. The mean gestational week at enrollment was 18 (±7) weeks. All women were already started on ART, and the median CD4 count was 404 (IQR: 228-609) cells/mm^3. About 30% (n=19) were on IPT at enrollment, and 85% (n=55) was not employed. All participants reported currently having a partner or spouse but 60% (n=38) was not living with partners.

In the follow-up visits, >95% reported taking ART. Of 65 infants, 1 (1.5%) was confirmed as HIV-positive, 47 (72.3%) were HIV-negative, 4 (6.2%) had indeterminate status, and 13 (20.0%) did not receive PCR tests. Over 90% (n=61) of participants ever breastfed their infants, and 67% (n=41) were still breastfeeding. While 51.5% (n=33) reported that they received somewhat or a lot of support from friends and family to remember taking medications, 95.2% (n=60) did so from healthcare providers ($p<0.001$). About 97% (n=62) people of patients who were on ART reported that they were informed about side effect and reasons to take ART while 85.7% (n=12) of people who were on IPT did so.

Table 5.2. Characteristics of the study population at enrolment among 65 HIV-positive individuals, South Africa*

N (%)	**N=65**
Age (years), Median (Q1, Q3)	27 (22, 31)
Time since HIV diagnosis (days), Mean (± SD)	55 ± 51
Gestational weeks, Mean (± SD)	18 ± 7
CD4 cell count (cells/mm^3),	582
Median (Q1, Q3)‡	404 (228, 609)
Marital status	
Married	6 (9.4)
Living with partner	20 (31.3)
Not living with partner	38 (59.4)
Employment status	
I work full time	5 (7.7)
I work part time or piece jobs	5 (7.7)
I am not employed	55 (84.6)
Number of adults living in the household	
0-1	24 (36.9)
2+	41 (63.1)
Number of children living in the household	
0-1	55 (84.6)
2+	10 (15.4)
Transportation	
On foot	36 (55.4)
Public taxi or bus	29 (44.6)
TB treatment history	
Yes	4 (6.2)
No	61 (93.8)
Currently on IPT	
Yes	19 (29.2)
No	46 (70.8)
Currently on CPT	
Yes	4 (6.4)
No	61 (93.6)

*Pearson χ^2 test (discrete variables), t-test (mean comparison for continuous variables) and Mann-Whitney test (median comparison for continuous variables) were used.
‡Some variables have missing data.

5.4.2 Preference weights in antepartum vs. postpartum period

Preference weights (i.e. utility) estimates for seven attributes are shown in Table 5.2. In the conditional logistic models, preventing HIV transmission had the highest coefficient (β=0.87, 95% CI: 0.64-1.11), followed by supporting family (β=0.75, 95% CI: 0.52-0.97) where positive coefficients represent positive preferences for these motivators. Keeping high CD4 counts showed the lowest coefficient (β=0.19, 95% CI: -0.04, 0.43) (Figure 5.2). In the postpartum period, the preference weights for most motivators significantly decreased. The coefficients for preventing HIV transmission and supporting family were 0.18 (95% CI: 0.00, 0.35) and 0.06 (95% CI: -0.12, 0.24) in the postpartum, respectively. Keeping high CD4 counts had slightly increased coefficient (β=0.39, 95% CI 0.21-0.57) in the postpartum period, compared to the antepartum period.

Table 5.3 Coefficients from conditional logistic and mixed logit regressions in the antepartum vs. postpartum

		Conditional Logit Estimates		Mixed Logit Estimates	
Benefits related to preventive therapies		**Antepartum** Coefficient (SE)[1]	**Postpartum** Coefficient (SE)	**Antepartum** Coefficient (SE)	**Postpartum** Coefficient (SE)
Preventing HIV transmission	Mean	0.87 (0.12)	0.18 (0.09)	1.73 (0.93)	0.19 (0.10)
	SD	—		1.64 (1.03)	0.15 (0.42)
Overall health	Mean	0.41 (0.12)	0.10 (0.09)	0.92 (0.53)	0.11 (0.10)
	SD	—		0.70 (0.77)	0.02 (0.38)
Supporting family	Mean	0.75 (0.11)	0.06 (0.09)	1.60 (0.85)	0.07 (0.10)
	SD	—		2.07 (1.20)	0.00 (0.18)
High CD4 counts	Mean	0.19 (0.12)	0.41 (0.09)	0.48 (0.31)	0.45 (0.11)
	SD	—		0.55 (0.91)	0.35 (0.21)
Disease control	Mean	0.67 (0.12)	0.24 (0.09)	1.39 (0.77)	0.26 (0.11)
	SD	—		0.63 (0.84)	0.37 (0.20)
Preventing infections	Mean	0.40 (0.12)	0.05 (0.09)	0.85 (0.49)	0.05 (0.10)
	SD	—		1.07 (0.81)	0.31 (0.22)
Preventing TB	Mean	0.44 (0.12)	0.21 (0.09)	0.84 (0.49)	0.23 (0.10)
	SD	—		0.51 (0.88)	0.01 (0.30)

[1] Mean β coefficients show estimated utility of each attribute, where positive coefficients indicate positive preference.

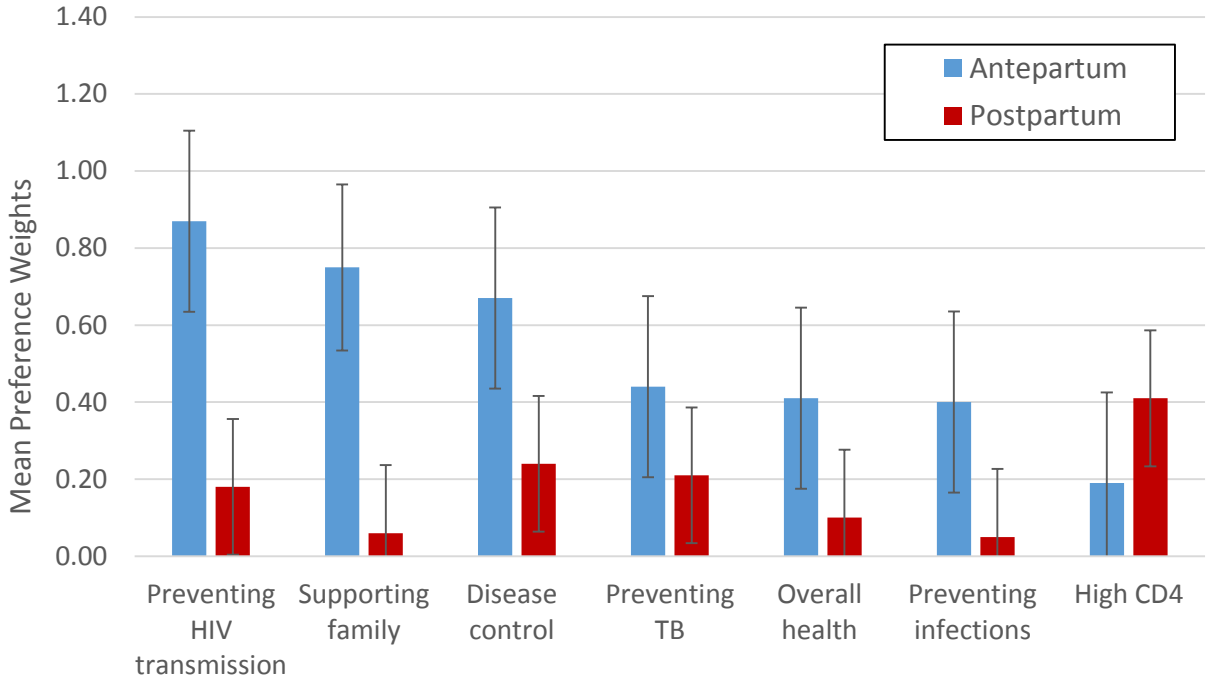

Figure 5.2. Preference weights estimated from conditional logit estimates for seven motivators to take preventive therapies among HIV-positive individuals in South Africa in the antepartum vs. postpartum period. The bar range represents 95% confidence interval for the mean preference weights.

The results were consistent in mixed logit models. In the antepartum, preventing HIV transmission had the highest mean coefficient (β=1.73), followed by supporting family (β=1.60), while high CD4 counts had the lowest mean coefficient (β=0.48). When the mean coefficients of the motivators were compared, the magnitude of utility gain was almost three times higher for preventing HIV transmission compared to high CD4 counts in the antepartum. In the postpartum, the mean coefficients for preventing HIV transmission and supporting family decreased to 0.19 and 0.07, respectively. Overall health, preventing infections and preventing TB had similar mean coefficients at both time periods.

When tested for the interaction with timing of visits, there were significant interactions between maternal motivators and timing of visits (Table 5.4). The preference weights for preventing HIV transmission and supporting family were 0.69 (±0.15) and 0.72 (±0.16) lower in the postpartum compared to in the antepartum, and the differences were statistically significant ($p<0.001$).

Table 5.4. Coefficients from mixed logit regressions with interactions terms for postpartum visits among HIV-positive pregnant women (N=65)*

Benefits related to preventive therapies	***Coefficient***	Mixed Logit Estimates
Preventing HIV transmission	Mean	**0.91 (0.13)****
	SD	0.30 (0.18)
Overall health	Mean	**0.43 (0.13)****
	SD	0.05 (0.91)
Supporting family	Mean	**0.78 (0.13)****
	SD	0.36 (0.16)
High CD4 counts	Mean	**0.21 (0.13)**
	SD	-0.06 (0.68)
Disease control	Mean	**0.69 (0.13)****
	SD	0.02 (2.33)
Preventing infections	Mean	**0.42 (0.13)****
	SD	-0.05 (0.95)
Preventing TB	Mean	**0.46 (0.13)****
	SD	0.00 (3.89)
Interaction with time		
Time*Preventing HIV transmission	Mean	-0.69 (0.15)**
Time*Overall health	Mean	-0.35 (0.16)**
Time*Supporting family	Mean	-0.72 (0.16)**
Time*High CD4 counts	Mean	0.20 (0.16)
Time*Disease control	Mean	-0.40 (0.16)**
Time*Preventing infections	Mean	-0.36 (0.16)**
Time*Preventing TB	Mean	-0.27 (0.16)

*Time was equaled to one for postpartum visits and to zero for antepartum visits in the model.
**p-value <0.05

5.5 Discussion

Pregnant women newly diagnosed with HIV faces the "triple burden" to accept that they are pregnant, newly diagnosed with HIV and need to make a life-long decision of initiating treatment.[99] Using a conjoint analysis, we demonstrate that prioritization of maternal motivations to take preventive therapies may change in the antepartum vs. postpartum periods. We found that HIV-positive pregnant women had high level of social motivation such as preventing HIV transmission to partners or supporting family compared to motivation related to their own health during pregnancy. However, the extent of such prioritization subdued in the postpartum. This is similar to previous findings that women initiating ART during pregnancy are likely to prioritize infant's health compared to their own health and have a strong motivation to take medications to prevent HIV transmission to their infants.[82,99,100] Also providing care for children and family was considered as an important motivator for women to remain healthy.[100] Our results underscore that while it is important to understand and support the social roles of HIV-positive pregnant women, more counseling needs to be provided with emphasis on the benefits of ART and IPT for maternal own health during antenatal care visits to ensure continued adherence to therapies.

In the postpartum, there was no clear ranking among motivators although prioritization for preventing HIV transmission or supporting family substantially decreased. These results need to be interpreted with caution. Since everyone in the study needed to make choices per question (i.e. there was no opt-out option), the lack of clear ranking among different motivators does not imply that their motivations to take preventive therapies may have decreased in the postpartum. Instead, this suggests after delivering a healthy baby mothers may have extended their motivation towards protecting their own health. Other studies similarly showed that HIV-positive pregnant women perceived their own health as a motivator to continue on therapies[101] and positive attitudes and perceived benefits towards treatment were reported as the facilitators for adherence

to ART and retention in care.[80,102] In our study, most of participants had been on ART on average of 2 months at enrollment thus may have not fully perceived the benefits of ART.

It is interesting that the most significant motivator in the postpartum was keeping high CD4 counts. It is possible that the participants gained better understanding about clinical implication of CD4 counts through repeated HIV counseling and regular clinic visits over time. A study among HIV-positive pregnant women in South Africa showed that providing CD4 count results might have helped mothers take HIV diagnosis more seriously and resulted in improved retention in care and adherence to ART after delivery.[99] Our study results highlight that counseling in the postpartum need to be geared towards promoting the benefits of ART and IPT for maternal health.

Other predictors of disengagement and/or poor adherence in the postpartum included non-disclosure of HIV status, feeling well, and inadequate knowledge about PMTCT.[8,99] About 80% of our participants disclosed their HIV status, and of those who knew their partners' HIV status, 77% of partners were HIV-positive. We did not see any changes in estimates by disclosure status nor partners' HIV status but this could be due to the small sample size. We fitted different models to estimate the associations. Mixed logit models have several advantages over conditional logit models as it allows the coefficients in the models to vary across individuals.[103] We found that convergence of mixed logit took much longer than in estimating conditional logit models due to the small sample size.

There are several limitations in our study. First, our study only considered benefits perceived at individual levels. Previous studies have shown that patient support is needed to be considered at multi-dimension including connectedness with health care providers and experience with care. Second, although our study results seem to reflect lack of maternal motivation in the postpartum period, however we cannot discount that mothers were less paying attention to the

surveys and choose more randomly in postnatal visits, resulting in overall lower scores. Third, our sample size of the study is quite small. In DCE, there is no standard sample size calculation. Lastly, interpretation of preference weights need caution. In our study, we did not have opt-out options thus participants had to make choices for each question. We used all positive statements thus the probability of choosing any one factor is naturally considered as greater than zero (i.e. better than choosing no factor).

5.6 Conclusion

In this study, we observed that prevention of HIV transmission and supporting family members were the most important motivators to take preventive therapies in the antepartum among HIV-positive pregnant women. Such prioritization subdued in the postpartum period, and keeping high CD4 count became a more important motivator. Incorporating the changes in preferences among HIV-positive women after delivery may enhance adherence and retention in care in this setting.

CHAPTER 6

Cost-effectiveness of isoniazid preventive therapy among HIV-positive pregnant women in South Africa

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6.1 Abstract

To estimate the incremental cost-effectiveness of universal isoniazid preventive therapy (IPT) and test-directed treatment of latent tuberculosis infection (LTBI) screening among HIV-positive pregnant women in South Africa, we estimated the cost-effectiveness of 12 months of IPT among HIV-positive pregnant in South Africa using a decision-analytic model from the health system perspective. We compared TST-directed IPT (performance of TST with delivery of IPT to women with positive results) with: 1) QuantiFERON-TB Gold In-Tube (QGIT)-directed IPT (performance of QGIT with delivery of IPT to women with positive results) and 2) Universal IPT (IPT offered to all HIV-positive women without screening for LTBI). Costs were measured empirically in 6 primary care public health clinics in Matlosana, South Africa in June-August 2016. Primary outcome was incremental cost-effectiveness ratio (ICER), expressed in 2016 US dollars per disability-adjusted life-years (DALYs) averted. We used time horizon of 1 year for the analysis. DALYs and costs were discounted at 3% per year. We estimated that 36 of 1,000 pregnant women would develop TB over the course of one year in the absence of IPT. TST-directed IPT reduced this number to 32 versus 30 with QGIT-directed IPT and 26 with universal IPT. The incremental cost-effectiveness ratio (ICER) of universal IPT, relative to TST-directed IPT, was $895/DALY averted while QGIT-directed IPT was dominated by universal IPT. ICER was most sensitive to the probability of developing TB, returning for TST reading and additional probability of IPT based on the positive results of LTBI screening. Providing IPT to all eligible pregnant HIV-positive pregnant women can be an effective strategy, especially when operational challenges of TST performance is substantial.

6.2 Introduction

Of 37 million people are living with HIV in 2015, tuberculosis is the leading cause of death among HIV-positive individuals. For HIV-positive individuals with suppressed immune system, the risk of converting latent tuberculosis infection (LTBI) to active TB can be high as 15% per year without antiretroviral therapy (ART). In South Africa, where HIV and tuberculosis are on-going public health challenges, about 37% of women who attended antennal care visits were HIV-positive in 2014,[12] and the prevalence of LTBI among females in reproductive age (15-49 years) is as high as 70%.[11] HIV-positive pregnant women are at greatly increased risk of TB reactivation, as high as 10-fold (relative to HIV-negative women) in some populations.[88]

Isoniazid preventive therapy (IPT) has been recommended as an important strategy as part of a comprehensive approach to end TB in endemic settings.[104] IPT is most effective among individuals with LTBI – typically diagnosed with the tuberculin skin test (TST) or interferon-gamma release assays (IGRAs)[90] – but testing for LTBI can cause some patients to be lost to follow-up. In South Africa, TST is recommended to determine the duration of IPT prescribed to people living with HIV (PLWH): 12 months if TST-positive or 36 months if TST is negative.[38] However, TST poses operational challenges as tuberculin needs to be refrigerated and patients are required to come back for reading the results. Studies have shown that up to 50% of patients may not return for TST reading.[35]

HIV-positive pregnant women may be a particularly relevant population for IPT delivery because antenatal care (ANC) visits represent a unique opportunity to screen for TB and provide preventive therapy. Maternal TB is a risk factor for maternal mortality, mother-to-child HIV transmission, and infant adverse health outcomes.[3–5] Thus it is crucial to prevent

reactivation of LTBI among HIV-positive pregnant women. However, only about 38% of eligible HIV-positive individuals were initiated on IPT in South Africa in 2015.[1] While TST poses operational challenges, healthcare workers might be hesitant to initiate eligible patients on IPT without any LTBI screening.[16,67] In this study, we sought to examine cost-effectiveness of universal IPT and test-driven IPT strategies, considering the short-lived protection effect of IPT in high TB and HIV endemic settings with targeted intervention for HIV-positive pregnant women.

6.3 Methods

6.3.1 Study design, intervention, and population

This was nested within an ongoing cluster randomized trial of TST versus QGIT in 14 South African clinics.[36,57] We conducted a cost-effectiveness analysis from the health system perspective in a hypothetical cohort of HIV-positive pregnant women in South Africa using decision analysis (Figure 1). We considered three strategies for providing IPT for 12 months to adult HIV-positive pregnant women presenting for routine antenatal care at public primary health centers: 1) TST-directed IPT IPT (performance of TST with delivery of IPT to women with positive results); 2) QGIT-directed IPT (performance of QGIT with delivery of IPT to women with positive results); and 3) Universal IPT (IPT offered to all HIV-positive women without screening for LTBI). We used duration of intervention at 1 year since it is the minimum duration of IPT recommended by the South African government when the results of TST are unavailable, and several studies have shown that IPT provision of 36 months has greater protective effect on TB incidence compared to 6 months but given the high loss to follow-up after delivery among HIV-positive women, 36 months may not be

feasible.[8] Also 12 months of IPT initiated during pregnancy would be continued to early post-partum when preventing TB has the greatest health effect for both mothers and infants. We used a proximal measure (TB cases and deaths averted). Primary model outcome was incremental cost-effectiveness (ICER) per disability-adjusted life-years (DALYs) averted.

Costs of providing IPT under different strategies were empirically measured using an "ingredients" (bottom-up) approach in 6 primary care public health clinics in Matlosana subdistrict, South Africa in June 2016-January 2017. The bottom-up approach was used to identify all resources used to perform LTBI screening and IPT management and valued to develop a unit cost. These six clinics (3 clinics randomized to provide QGIT and 3 clinics continued to provide TST as a routine LTBIT screening) were chosen to represent wide ranges of geographic locations and volume of patients at clinics. We collected the costs of overheads, building space, equipment, staff, and consumables related to IPT initiation and management as well as diagnostics for TST and QGIT. All costs were adjusted for inflation using the consumer price index for South Africa and converted to US dollars using the 2016 exchange rate (1US$=ZAR14.72 Rand).

We used the combination of interviews, documentation reviews at subdistrict offices, and publically available information for products to calculate costs. Overheads costs and building space were allocated based on proportional space required and percentage of time devoted to LTBI screenings and IPT management. These information was obtained from time and motion studies, which counted the number and type of staff and estimated the time spent on TB screening and IPT prescription. Floor plans were obtained from all six clinics, and the values of building and facilities were estimated based on the average construction cost to build a public clinic per square meters.[105] Equipment and furniture inventories were obtained from subdistricts offices and directly counted at clinics. Cost of training was calculated based

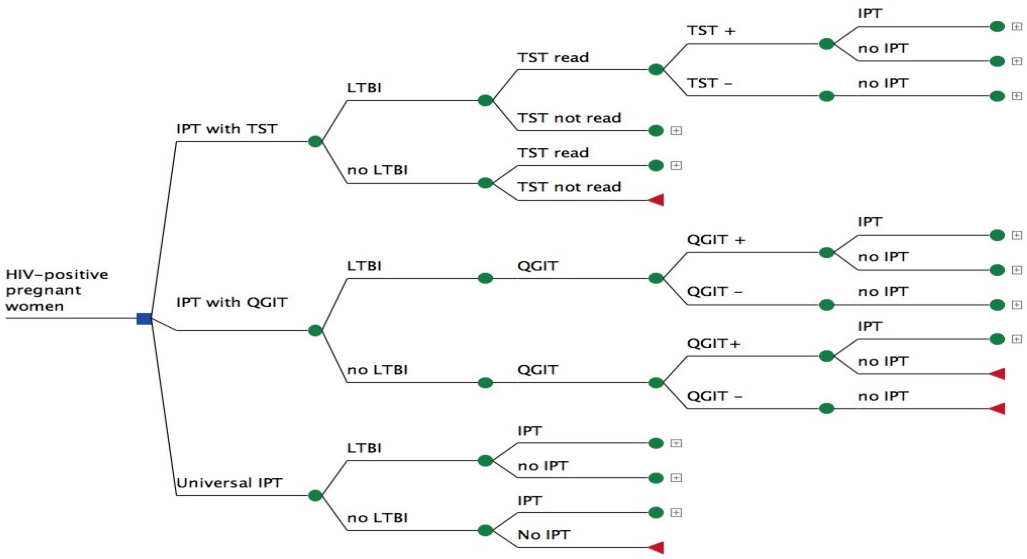
on the reported time spent on TST performance and IPT prescription during subdistrict or nurse-initiated and managed antiretroviral treatment (NIMART) trainings during the year prior to the interview. Current annual salaries of staff were obtained from subdistrict offices. Costs related to TB and DILI treatment was estimated from the published literature as well as from South African drug costs. For QGIT, we used the processing price of biosamples by the national health laboratory service (NHLS) and the QGIT kit price charged by a QIAGEN company. All costing was measured in Both DALYs and costs were discounted at 3%.

6.3.2 Empiric costing

Cost-effectiveness was measured as the incremental cost-effectiveness ratio (ICER) relative to TST-directed IPT (the baseline strategy) and expressed in units of 2016 US dollars per DALY averted. We also chose a time horizon of 1 year to analyze the health outcomes (TB and DILI cases) in the same year, followed by additional 6 months if TB treatment was needed. Recent studies in high TB burden settings showed that the protection from IPT was quickly lost within 6-12 months due to reactivation of persistent latent infection and reinfection from ongoing community transmission of LTBI[106,107] so a time horizon of 1 year most likely reflect the effectiveness of IPT in a high TB burden setting in a conservative way. We assumed that 1 X-ray, 2 blood tests, and 2 liver functions tests were conducted for those with mild DILI, and 1 X-ray, 3 blood tests, and 3 liver functions tests for severe DILI with 1 week of hospitalization.[108] We also estimated the costs incurring to health system when the interventions would scale up to all eligible HIV-positive pregnant women per year in South Africa, which was estimated as 324,000 per year with birth rate of 1.8 million per year and 30% HIV prevalence among those attending public antenatal care clinics in the South African health system.[2] We did not include ART costs as part of intervention costs since we wanted to compare the incremental costs of TB screening and IPT only. We used WHO-suggested

country-specific willingness to pay (WTP) thresholds at $20,043, defined as three times of the national annual gross domestic product per capita in South Africa ($6,681) per DALY averted. Model was built in TreeAge (Williamstown, Massachusetts, USA).

(A)



(B)

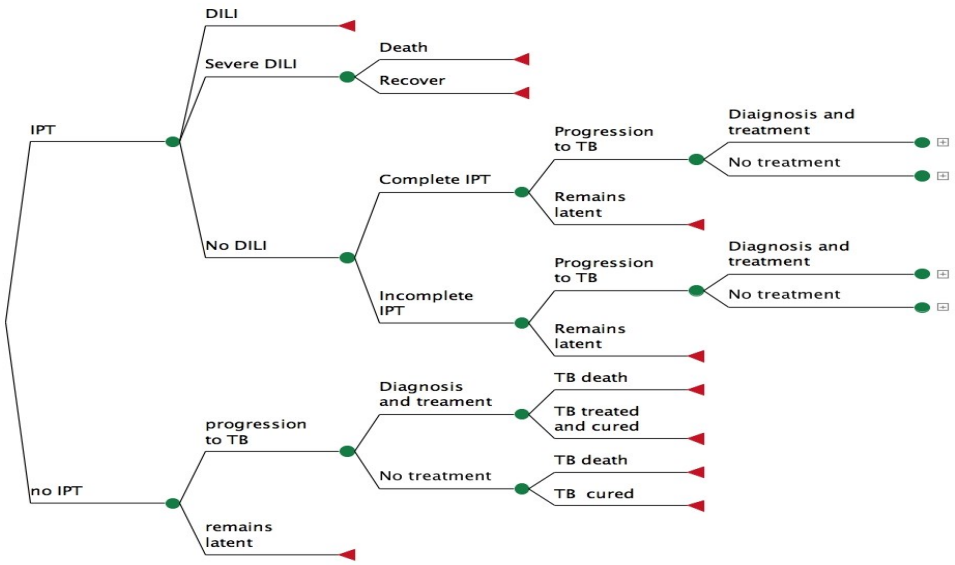


Figure 6.1. Model diagram of decision analysis model in the target population of HIV-positive pregnant women in high TB burden settings. In all three arms in (A), the subtrees continue to progress to the corresponding trees by IPT initiation status in (B).

6.3.3 Epidemiologic, diagnosis and treatment parameters

Parameters related to epidemiological outcomes were estimated from the scientific literature, giving preference to studies of HIV-positive pregnant women in South Africa, when available (Table 5.3). Using the values estimated from our study and literature review, we assumed 50% of eligible patients initiated IPT with a range of values (22%-77%) in sensitivity analyses. We first assumed that the same proportion of eligible patients would initiate IPT if tested positive then ran sensitivity analyses that potentially more people compared to universal IPT arm would initiate IPT based on the results of TST or QGIT. There could be two mechanisms for this. Patients may actually prefer to have a test before initiating a treatment than no test at all.[109] Studies have also shown that healthcare workers were concerned about induced drug resistance due to IPT and difficulty of ruling out active TB prior to IPT initiation.[16]

We estimated DALYs among 1,000 HIV-positive pregnant women at age of 25 years, which is the median age of antenatal HIV-positive women presenting at public clinics in South Africa.[2] We assumed that HIV-positive pregnant women experienced disability associated with HIV on ART,[110] that those who initiated IPT had a defined risk of severe hepatotoxicity incurring additional costs and risk of mortality,[111–114] and that HIV-positive pregnant women at age of 25 years had an average life expectancy of 33.9 years in the absence of TB.[115] We assumed that every woman was on ART and that here was slight disability-associated with taking IPT, based on the disability weight for daily chronic medication and worry.[110] DALYs were then calculated as the combination of years of life lost plus years of life with disability, with future outcomes discounted at 3% per year.

Mild toxicity was defined as ALT grade 3-4 and did not change duration of treatment or treatment efficacy. Severe DILI was defined as AST or ALT > five times the upper limit of normal level, leading to permanent discontinuation of treatment and 1 week of hospitalization. We assumed that severe DILI have occurred one month after IPT initiation on average. There are limited data on hepatotoxicity of IPT among HIV-positive pregnant women thus data from observational studies among pregnant women if available or outcomes from other randomized clinical trials was used.[111–114] We assumed that incompletion of IPT occurred at 6 months after initiation on average and there was no protective effect of IPT after discontinuation. In our setting of high annual risk of TB re-infection, we conservatively assumed that the effect of IPT would only last while the patient was on IPT and impact on TB incidences. Patients developing active TB could be diagnosed and treated based on current case-detection and treatment rates in South Africa.[1] We did not include any additional costs due to HIV or ART costs, assuming that all women were already diagnosed.

6.3.4 Sensitivity and uncertainty analysis

We performed a one-way sensitivity analysis, varying key parameters by ±75% when data on the range of parameters were limited. The outcomes were highly sensitive to proportion of additional initiation IPT in test-driven strategies and proportion of TST reading done thus we performed two-way sensitivity analysis varying these key parameters simultaneously. We also ran a scenario analysis where the probability of additional initiation of IPT has increased to 30%. Probabilistic sensitivity analysis (PSA) using Monte Carlo simulations was conducted to simultaneously vary all parameters across their ranges to generate 95% uncertainty ranges (UR) for outcome estimates of costs, DALYs, and cost-effectiveness. These results were also used to generate a cost-effectiveness acceptability curve.

6.3.5 Ethical considerations

This study was approved by the Institute Review Board of Johns Hopkins School of Medicine, Baltimore, Maryland, USA and the University of the Witwatersrand Human Research Ethics Committee.

Table 6.1. Epidemiologic, diagnostic and treatment parameters used in sensitivity analyses among HIV-positive pregnant women in South Africa

Input variable	Base-case value	Low	High	Source
Prevalence of LTBI	0.767	0.454	0.932	11
Risk of TB with LTBI (per year)*	0.047	0.017	0 .074	4,116,117
Relative risk to develop TB with IPT	0.38	0.06	0.57	6
Proportion of IPT initiation without LTBI screening	0.50	0.22	0.77	Study; 21
Additional proportion of IPT initiation with LTBI screening	0	0	0.5	Assumption
Probability of return to TST reading	0.7	0.5	0.9	4,35
Proportion of IPT completion†	0.645	0.47	0.88	21,90,118
TST performance				
Sensitivity (.10 mm)	0.60	0.45	0.67	4,119,120
Specificity (.10 mm)	0.91	0.68	1	119
QGIT performance				
Sensitivity	0.61	0.41	0.75	120,121
Specificity	0.90	0.675	1	120,121
DILI and TB				
IPT-related DILI‡	0.03	0.002	0.15	111–114
Proportion of severe DILI	0.014	0.00005	0.029	111,112,114,122
Probability of death due to severe DILI	0.053	0.0001	0.1	112
TB treatment (%)				
TB detection	0.64	0.48	0.80	1
TB mortality probability if untreated	0.50	0.375	0.625	1
TB treatment-related mortality	0.083	0.064	0.107	1,123
Disability weights				
Mild-IPT induced hepatotoxicity	0.15	0.05	0.3	
Severe IPT-induced hepatotoxicity‡	0.6	0.1	0.9	34
Active TB treatment	0.1	0.01	0.25	
Active TB (HIV+ co-infection)	0.408	0.274	0.549	
HIV+ (receiving ART)	0.078	0.052	0.111	
IPT	0.049	0.031	0.053	
Life expectancy at initiation of ART**	33.9	31.5	36.5	115

*We modeled progression to active TB within 1 year of model entry for decision analysis.
†For those who did not complete 12-month IPT, we assumed that they received about 6 months of IPT, which resulted in a relative risk reduction of 0.31 in the base case (range 0.11-0.385).
‡IPT-induced severe hepatotoxicity is defined as hepatitis grade 3 or higher.
**Life expectancy at initiation of ART was calculated at median age of 25 years among HIV-positive women.

Table 6.2. Cost analysis of screening and treatment of LTBI in South Africa, 2016

Description	Base-case value (US$)	Low	High	Source
Cost of TST	**2.19**	1.64	2.74	
Nursing staff time (application and reading)	0.45			
Consumables and materials (gloves, syringes, needles, box for syringes)	1.14			Study*; 33
Training unit cost	0.45			
Overhead unit cost	0.06			
Cost of QGIT	**54.38**	40.79	63.97	Study
Nursing staff time	1.20			
Consumables and materials	11.44			
Lab cost	36.72			
Sample transport cost	4.95			
Overhead unit cost	0.07			
Costs of IPT				
Isoniazid 300mg/day (monthly)	0.90	0.70	1.10	Study
Initial consultation	1.89	1.40	2.40	Study
Follow-up outpatient consultation per visit	1.73	1.30	2.20	Study
Total cost of IPT treatment (12 months)	31.72	11.00	64.90	Calculated; 31
Cost related to DILI and TB treatment costs				
Blood count tests	9.48	2.76	10.86	124,125
Liver function test	8.92	4.76	27.68	124–126
Sputum test	2.00	1.03	2.20	124,127,128
Chest Xray	18.91	5.03	23.46	124,127,128
Outpatient follow-up at tertiary hospital	18.42	6.73	39.71	31,129
Hospitalization per diem	109.38	45.60	126.64	Study; 31,129
Active TB treatment	149.48	113.58	269.93	33,124

*Data was based on the data collected from study clinics and local hospitals.

6.4 Results

6.4.1 Cost and cost-effectiveness of IPT provision and LTBI diagnostics

The average total cost per patient in universal IPT, QGIT-directed IPT, or TST-directed IPT arms was $23.38, $67.50, and $12.70, respectively (Table 3). Providing IPT to all HIV-positive pregnant women had the highest cost for IPT ($12.97) and IPT-related DILI treatment costs ($6.99) but had slightly lower cost for TB treatment ($2.48) than providing IPT to women with positive results of QGIT or TST. The median costs per 1000 patients including diagnostic, IPT, IPT-related DILI treatment and TB treatment were $23,383 (IQR $20,480-$26,479) in universal IPT, $76,584 (IQR $65,486-$94,698) in QGIT-directed IPT and $12,069 (IQR $10,803-$13,653) in TST-directed IPT, respectively. To scale up the intervention to all HIV-positive pregnant women in South Africa of approximately 324,000 would cost about $7.6, $5.1 and $25.8 million (Table 6.4). Compared to universal IPT arm, QGIT-directed arm was absolutely dominated.

Table 6.3 Average total cost per patient

	Universal IPT	IPT with TST	IPT with QGIT
Diagnostic	0.94	2.94	54.84
LTBI treatment	12.97	4.36	6.37
IPT-related DILI	6.99	2.35	3.43
TB treatment	2.48	3.04	2.86
Average total cost per patient (2016 US$)	23.38	12.70	67.50

Table 6.4 Expected costs, DALYs averted, and incremental cost-effectiveness

	Total cost	Active TB cases	Deaths from TB or DILI	DALYs	Cost per DALYs averted
TST	12,648	31.8	7.5	174	
Universal IPT	23,382	25.9	6.4	162	
Incremental universal IPT vs. TST	*10,734*	5.9	*1.1*	*-12*	*895*
IPT with QGIT	67,504	29.9	7.1	168	
Incremental QGIT vs. TST	*54,856*	*1.9*	*0.4*	*-6*	*9143*

*324,000 births per year estimated to occur among HIV-positive pregnant women

**Without any intervention, xx number of cases would have occurred per 1000 individuals.

Among 1,000 women in the cohort, 767 were assumed to have LTBI, of whom 36 would develop reactivation of TB and 8 would die of TB in the absence of IPT. In the TST-directed IPT strategy, 168 (16.8%) of 1,000 women were assumed to receive IPT, reducing the number of TB cases to 31.8 and TB deaths to 7.5. Of these, 7.3 patients without LTBI would be started on IPT due to false-positive results, of whom 0.3 patient was assumed to experience mild or severe DILI and 0.01 to die due to DILI. Under the universal IPT strategy, 500 (50.0%) of 1,000 women were assumed to receive IPT, reducing the number of TB cases to 25.9 and TB deaths to 6.5 patients. 116 patients without LTBI would be started on IPT, of whom 5.1 patient was assumed to experience mild or severe DILI and 0.09 to die due to DILI. The incremental cost-effective ratio (ICER) was $895/DALY averted in universal IPT and $9,143/DALY averted in QGIT-driven IPT.

6.4.2 Sensitivity analyses

Parameters that were found to have the greatest effect on the incremental cost-effectiveness of universal IPT relative to TST-directed IPT in one-way sensitivity analysis

are shown in Figure 5.2. Specifically, the ICER was most sensitive to estimates of the probability of progression from LTBI to active TB. When the risk of progression to active TB increased to 7.4%, the ICER increased to $32,412 per DALY averted. ICERs were also sensitive to prevalence of LTBI. When the risk of reactivation fell below 1.8%, universal IPT became less effective than TST-directed IPT because the risk of side effects outweighed the benefit of IPT. When prevalence of was low as 45.4%, universal IPT also became less effective compared to TST-directed IPT.

Results of PSA are shown in Figure 5.3, with median ICERs of $985/DALY averted (95% CI $235-$14,988) based on 10,000 Monte Carlo simulations of the model. The cost-acceptability curve is shown in Figure 5.4. At a WTP threshold of US$20,043/DALY averted in the context of South Africa, 88% of simulations favored the universal IPT arm. The QGIT arm had the mean ICERs of $9,830/DALY averted (95% CI $5,048-$30,627) compared to TST arm, but it was dominated when compared to the universal IPT arm.

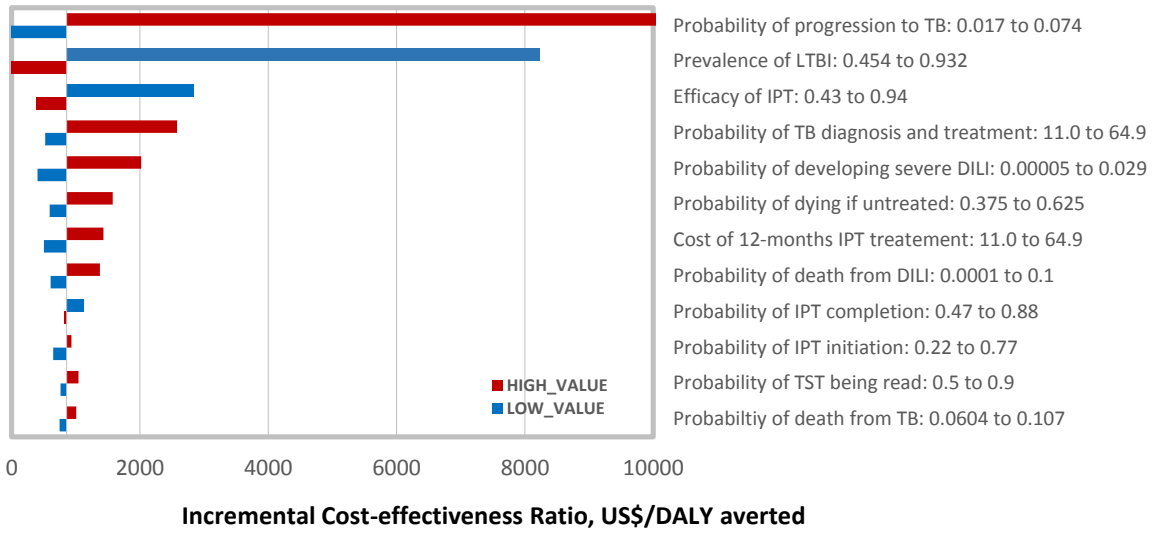


Figure 6.2. Tornado diagram for one-way sensitivity analysis for incremental cost-effectiveness ratio per DALY averted, comparing universal IPT arm vs. TST arm. Red and blue bars represent the highest and lowest values in the range in each variable.

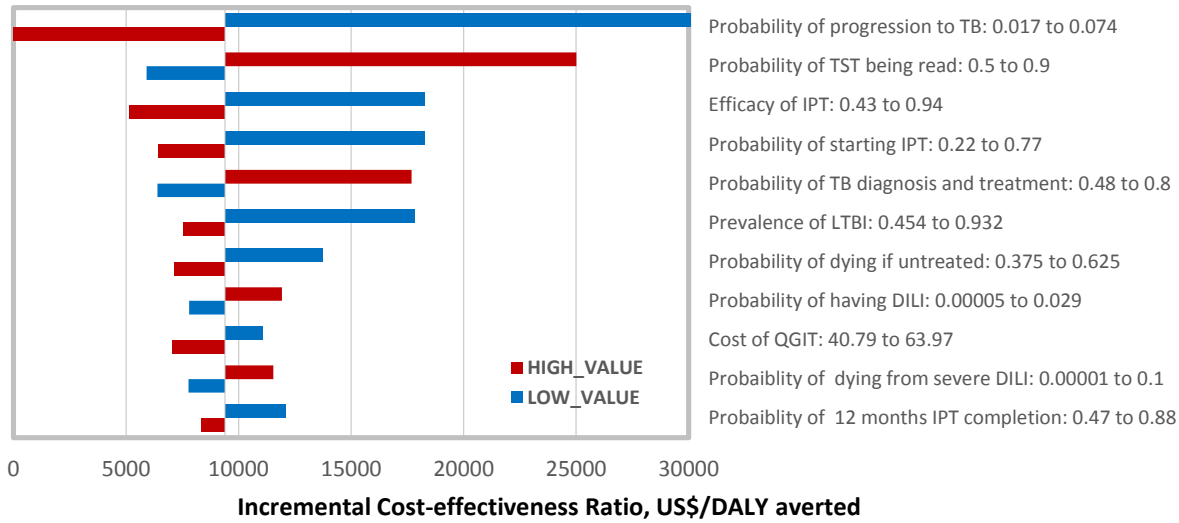


Figure 6.3. Tornado diagram for one-way sensitivity analysis for incremental cost-effectiveness ratio per DALY averted, comparing QGIT arm vs. TST arm. Red and blue bars represent the highest and lowest values in the range in each variable.

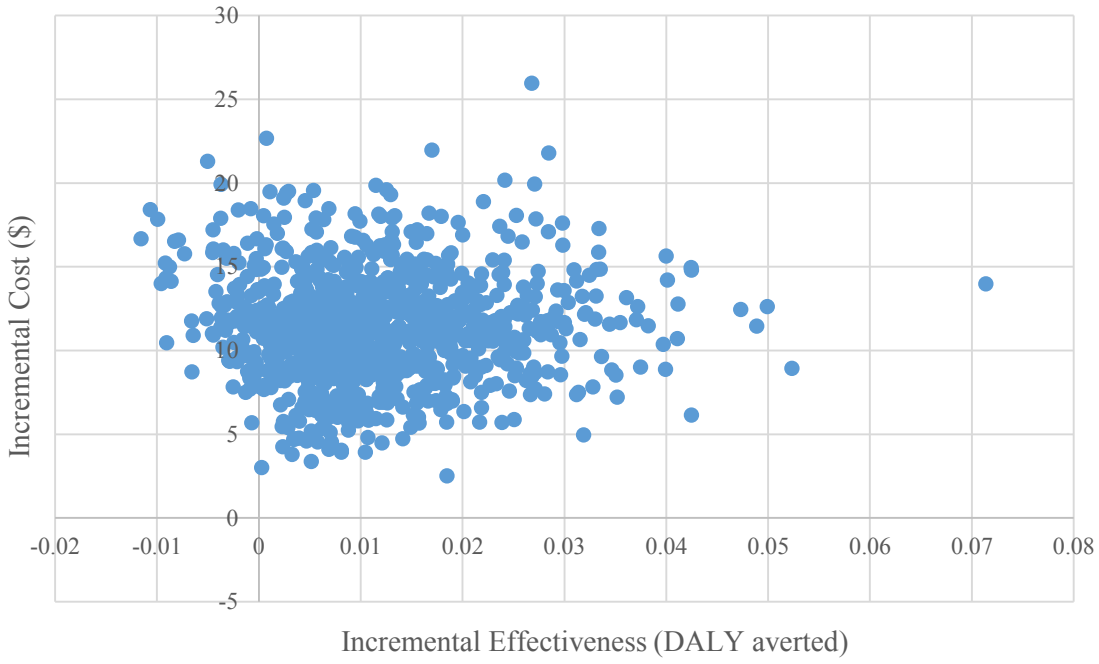


Figure 6.4. Point diagram resulting from the probabilistic sensitivity analysis, comparing universal IPT arm vs. TST arm under 10,000 monte carlo simulation

6.4.3 Impact of TST reading and proportion of additional initiation of IPT

We ran several sensitivity analyses for the performance of TST with IPT given to positive TST results. First, when the probability of additional IPT initiation in TST-driven IPT arm increased to 30%, the ICER increased to $1,025/DALY averted in universal IPT, compared to TST-driven IPT. Figure 5.5 shows ICERs in the two-way sensitivity analyses comparing universal IPT vs. TST-directed IPT under different probability of TST reading done and additional IPT initiation in TST-directed IPT. When the probability of TST reading done is low (<50%), universal IPT had the ICER less than $1,000/DALY averted regardless additional probability of IPT initiation in TST-driven IPT arm. as the probability of TST

reading done and additional initiation of IPT increase, the ICER increased further and could result in cost-saving for TST-driven IPT strategy.

Probability of TST reading returned	Probability of additional IPT acceptance										
	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
0	645	645	645	645	645	645	645	645	645	645	645
0.1	662	663	664	665	666	668	669	670	672	673	674
0.2	681	684	687	690	693	697	700	704	708	711	716
0.3	704	710	715	722	728	735	743	751	759	768	778
0.4	732	741	751	763	775	788	803	820	839	860	885
0.5	766	781	799	819	841	868	899	936	980	1036	1107
0.6	809	834	863	899	943	997	1068	1163	1297	1502	1850
0.7	865	906	958	1025	1117	1249	1454	1820	2650	6382	
0.8	940	1010	1107	1250	1486	1943	3213	24652			
0.9	1048	1174	1379	1768	2794	13020					
1	1214	1473	2036	4209							

$0-1000 $1000-2500 $2500-5000 >$5000 Cost saving

Figure 6.5. Two-way sensitivity analysis diagram comparing probability of LTBI and probability of starting IPT when probability of TST being read is at 0.90 across all arms

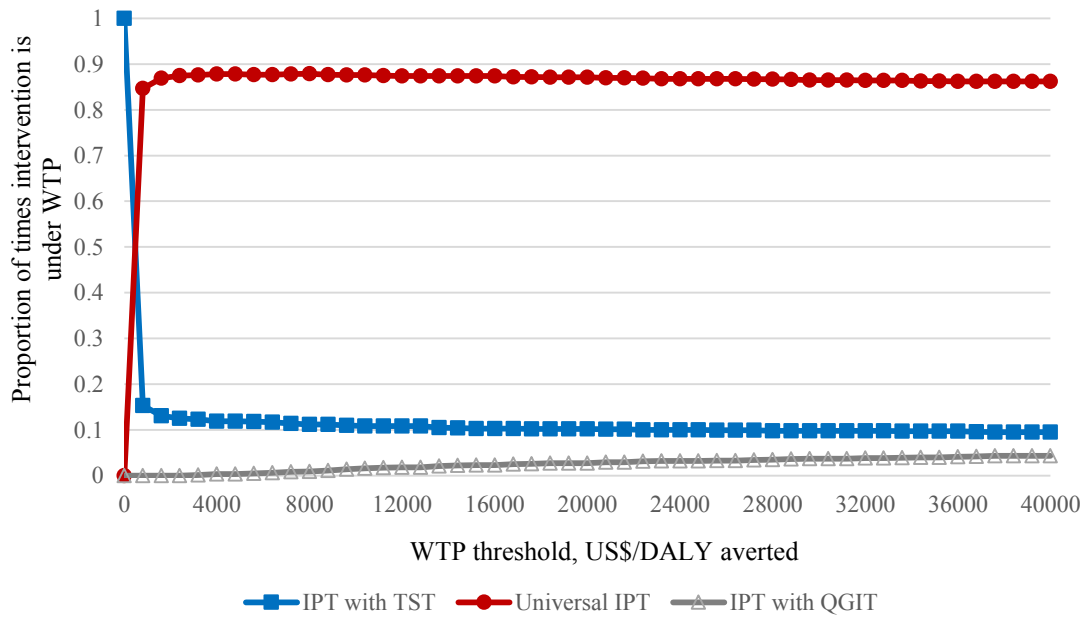


Figure 6.6. Cost-acceptability curve for universal IPT, TST-directed IPT, and QGIT-directed IPT by different willingness-to-pay (WTP) threshold for ICER.

6.5 Discussion

Usage of TST has been used as a traditional way to test LTBI in resource-limited settings. Our results suggest that universal IPT for 12 months, compared to TST-driven IPT strategy in which IPT is only provided to TST-positive patients, has ICER of $895/DALY averted in high TB and HIV burden settings with potentially rapid loss of protective effect from IPT upon cessation of IPT. We have taken a conservative approach where the protective effect of IPT would last only for 12 months. Several sensitivity analyses were additionally performed and showed that the incremental effectiveness with additional cost spent on IPT might differ significantly, depending on the context of settings. With slightly higher DALY due to IPT, there are also net gains by preventing TB cases and TB deaths. When compared to universal IPT arm, QGIT-directed arm was absolutely dominated.

This study is meaningful in several ways. First, we empirically measured the costs. The cost of TST was quite low compared to previously reported values. We did not account the impact of patient volumes on the cost of tuberculin; each vial contains 10 tests and needs to be refrigerated and used within one month upon opening. Thus low TST performance may increase the cost of TST. Although professional nurses were provided training on TB and HIV screening and management on a regular basis by the district office, training time spent on TB screening and IPT performance was very low. In the six clinics, the number of staff who could perform TST quite varied. In some clinics, only TB nurses were performing TST while any professional nurse could perform TST in other clinics.

Second, we estimated the cost-effectiveness of IPT HIV-positive pregnant women and estimated the cost and effectiveness for scaling up this intervention to all potentially available women in the context of South Africa with high HIV burden. A recent study in India reported that IPT regardless of CD4 cell count among HIV-positive pregnant women

was cost-effective compared to no IPT, which is the standard of care in India, and also found that providing IPT regardless of IPT was cost-effective compared to TST-driven strategies [129]. However, this study assumed the protection of IPT would last over a person's life time horizon of 20 years. Second, several studies examined cost-effectiveness of IPT among PLWH in low- or middle TB-burden countries with a rather long time horizon for analysis of 20 years or longer [29,31,126] but few studies were conducted in high endemic settings for both TB and HIV. As studies have continuously shown that the effect of IPT is quite limited upon cessation of IPT in high TB burden settings due to reactivation or reinfection, shorter time frame for analysis seems to be more appropriate. In this study, when a 1 year of time horizon was considered, universal IPT was still considered cost-effective.

Many previous studies have shown that providing IPT is cost-effective to avert TB cases, especially among HIV-positive individuals.[29,33,129] Given the evidence of effectiveness of IPT, the South African government originally recommended to initiate IPT regardless of TST in 2011. However, the re-introduction of TST in the new guideline in 2013 without sufficient communication and training in local hospitals have been considered as a barrier to IPT implementation.[16]

In the case scenario of 30% additional initiation of TST, we found that the ICER in universal IPT was $1,025/DALY averted but when majority of people placed with TST come back, the probability of additional IPT initiation among patients with TST-positive results is critical in terms of cost-effectiveness. However, when many patients may not come back for TST reading, even at the best scenario of initiating IPT for 100% based on TST-positive results compared to 50% IPT initiation in universal IPT arm, the highest ICER with 50% of TST reading done would be $1,107/DALY averted. Thus when there are operational challenges of TST, universal IPT could be an effective strategy given resources required.

There are several limitations in this study. Although we found that the intervention was cost-effective compared to the conventional GDP threshold, different thresholds can be applied to determine cost-effectiveness and may not apply to other interventions. Also, we assumed that every pregnant woman was on ART as observed in our study as well as in the national South African health report.[105] However, maternal ART coverage may decrease in the postpartum period and other settings may have lower ART coverage among pregnant women. We considered the effect of IPT separately but there could be synergetic effect between ART and IPT to reduce TB incidence.[130] We also assumed that the efficacy of IPT is similar in antepartum and postpartum period and people won't be lost to follow up in the postpartum period. However, many studies have shown that pregnant women are less likely to be retained in the care after delivering a healthy baby. We assumed that the same percentage of additional people would be initiated on IPT in the QGIT arm but this assumption may not be valid. Currently, the trial is on-going whether QGIT linked to routine CD4 test counting would allow more people to be initiated on IPT in the same clinics.

6.6 Conclusion

In this study, we showed that universal IPT can be an effective strategy for IPT provision, especially when operational challenges of TST performance is substantial. As IPT is considered as an important strategy to end TB, universal IPT should be considered as a potential option in resource limited settings with high TB burden.

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CHAPTER 7

Conclusion

7.1 Summary of dissertation

In this dissertation, we examined the changes in priorities related to preventive therapies among HIV-positive pregnant women in South Africa using conjoint analysis and best-worst scaling methods. Mothers prioritized trust in healthcare providers, followed by living a long life. Fear of unintended disclosure of HIV status due to daily pill take was least prioritized. The overall ranking of attributes was similar by IPT initiation at enrollment. When priorities were compared before and after delivery, mothers reported that they had significantly greater difficulty in taking medications on a daily basis in the postpartum period. On the other hand, maternal motivation to take preventive therapies was most prioritized for preventing HIV transmission to a partner or keeping healthy for family, compared to other motivators related to their own health in the antepartum. However, the extent of such prioritization subdued in the postpartum and keeping high CD4 count was considered as the most important motivator in the postpartum. We also found that universal IPT can be an effective strategy, especially if application and reading of TST poses substantial operational challenges.

7.2 Limitations

There are many limitations in this thesis work. First, the study had about 25% loss to follow-up in the overall cohort; in addition, the DCE instrument (Chapter 5) was added into the study questionnaire after the study enrollment was half completed thus the sample size at baseline was quite small. When people lost to follow up were compared to those included in the analysis, we observed no systematic difference. We tried to contact and track down mothers who missed scheduled clinic visits and complete follow-up visits as needed. However, about one-third of those lost to follow up relocated to different location and another one-third could not be reached further. Those who were potentially disengaged from the care may have had different priorities compared to the ones included in the analysis. Secondly, we tried to enroll all eligible participants at the study clinics but due to limited number of study staff we could have missed some participants presented at clinics. Third, although the instrument development was based on the qualitative interviews which were conducted in the same 14 clinics, only few pregnant women were included as part of the interviews. We did perform literature reviews to select the motivators mostly relevant to maternal decisions but there could be other motivators not included in this study. Fourth, we did not have the data on viral suppression in the postpartum and the self-reported adherence could have been overstated. Also we did not capture the duration or completion of IPT among those who were prescribed to take INH. The proportion of people receiving IPT was low in the both antepartum and postpartum periods thus we could not statistically compare changes in the adherences.

7.3 Public health implications

This study provides important insight into the patient-centered delivery of preventive therapies among HIV-positive pregnant women in South Africa and potentially in other high HIV and TB burden settings. Although HIV-positive women after delivery prioritize attributes related to infants' health, they have high perceived benefits of medications for their own health in the postpartum period. Similarly, pregnant women newly diagnosed with HIV might be more motivated to take therapies for partners or family members in the antepartum, such relative importance decreases in the postpartum and health promotion messages for high CD4 counts or maternal health benefits would be potentially well received. Our study results suggest that if IPT is provided to HIV-positive pregnant women with adequate counseling and support, it is likely that the uptake of IPT would be improved both in the antepartum and postpartum periods. Targeted counseling and interventions to emphasize the benefits of ART and IPT in the postpartum could be important. We demonstrate that application of stated preferences methods could be an alternate way to elicit patients' preferences in other resource limited settings. Finally, as IPT is considered as an important strategy to end TB, universal IPT can be a potential option to maximize the benefits of IPT at population level especially in high HIV and TB burden settings.

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7.5 Curriculum Vitae

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RESEARCH KEYWORDS

HIV, Tuberculosis, maternal and child health, causal mechanisms, stated preferences, patient-centered outcomes, cost-effectiveness, cohort studies, longitudinal data analysis, implementation science, operational research, qualitative analysis, clinical interventions, modeling, sub-Saharan Africa

EDUCATION

2017 **Johns Hopkins Bloomberg School of Public Health,** Baltimore, MD, USA
PhD Candidate in Epidemiology (Concentration: Infectious Disease)
Thesis Title: *Preferences and cost-effectiveness of HIV and TB preventive therapies among HIV-positive pregnant women in South Africa*
Advisor: David W Dowdy, MD PhD
Thesis Committee: Colleen F Hanrahan, PhD and Susan Sherman, PhD

2011 **Mailman School of Public Health, Columbia University**, New York, NY, USA
Master of Public Health, Epidemiology

2009 **Carleton College**, Northfield, MN, USA
Bachelor of Arts, Chemistry, *Magma cum laude*

2008 **Sciences Po (Institut d'Etudes Politiques de Paris)**, Paris, France
Exchange student program: *Public Health in Europe: Policies and Institutions*

PROFESSIONAL EXPERIENCE

2016 - present **Research Assistant**
Department of Medicine, Johns Hopkins School of Medicine
Project: Mass chest X-ray TB screening in correctional facilities in South Africa
Principal Investigator: Chris Hoffman, MD

2016 - present **Research Assistant**
Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health
Project: Comparative effectiveness/implementation of tuberculosis case finding in rural

South Africa
Principal Investigator: David W Dowdy, MD PhD

2014 - present **Research Assistant**
Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health
Project:
- Patient and provider preferences for preventive therapies in HIV infected persons
- Quantiferon Gold Test for detecting tuberculosis infection in HIV/AIDS patients in South Africa

Principal Investigators: Jonathan Golub, PhD and Neil Martinson, PhD

2014 - 2015 **Research Assistant**
Department of Health, Behavior and Society, Johns Hopkins Bloomberg School of Public Health
Project: Access to HIV/AIDS Care in USA
Principal Investigator: Catherine Maulsby, PhD

2013 - 2014 **Research Assistant**
Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health
Project: Systematic review for global HIV incidence among female sex workers
Principal Investigator: Andrea Witz, PhD

2011 - 2013 **Research Worker**
Gertrude H. Sergievsky Center, Columbia University College of Physicians & Surgeons
Project:
- Zambia Exclusive Breastfeeding Study (ZEBS)
- Support for relactation among HIV-positive women in South Africa
- Oligosaccharide composition of breast milk in HIV-positive women

Principal Investigator: Louise Kuhn, PhD

HONORS & AWARDS

EXTERNAL AWARDS

2015 Mokam Science Research Scholarship, Mokam Research Institute, Seoul, Korea
2015 Network Modeling for Epidemics Scholarship, University of Washington
2012 Young Investigation Award, 19th Conference on Retroviruses and Opportunistic Infections
2010 Student Paper Award, the NorthEast SAS Users Group (NESUG) Conference

JOHNS HOPKINS SCHOOL OF PUBLIC HEALTH

2016 Doctoral Thesis Research Scholarship, Department of Epidemiology
2016 Student Travel Award, Department of Epidemiology

2016 Charlotte Ferencz Scholarship *for contribution in the field of maternal and child health,* Department of Epidemiology
2015 Marilyn Spivak Menkes Award *for contribution to the department and student life,* Department of Epidemiology
2015 Global Health Day Poster Session, 3rd Place, Center for Global Health
2014 Global Health Established Field Placement, Center for Global Health

COLUMBIA UNIVERSITY
2011 Anna C. Gelman Award for Excellence in Epidemiology, Department of Epidemiology

PUBLICATIONS

PEER-REVIEWED JOURNAL ARTICLES

1. **Kim HY**, Lebina L, Milovanovic M, Taruberekera N, Dowdy DW, Martinson NA. Evaluating the cost of adult voluntary medical male circumcision in a mixed (surgical and PrePex) site compared to a hypothetical PrePex-only site in South Africa**.** *Global Health Action* 2015; **8**:29116
2. Kuhn L, **Kim HY**, Hsiao L, Nissan C, Kankasa C, Mwiya M, et al. Oligosaccharide Composition of Breast Milk Influences Survival of Uninfected Children Born to HIV-positive Mothers in Lusaka, Zambia. *The Journal of Nutrition* 2015; **145**:66-72.
3. Nyati M, **Kim HY**, Goga A, Violari A, Kuhn L, Gray G. Support for relactation among mothers of HIV-positive children: a pilot study in Soweto**.** *Breastfeeding Medicine* 2014, 9(9):450-7
4. Chan CS, **Kim HY**, Autran C, Kim JH, Sinkala M, Kankasa C, et al**.** Human Milk Galectin-3 Binding Protein and Breastfeeding-Associated HIV Transmission*. Pediatr Infect Dis J* 2013, Jul 30.
5. Kuhn L, **Kim HY**, Walter J, Thea DM, Sinkala M, Mwiya M*, et al.* HIV-1 Concentrations in Human Breast Milk Before and After Weaning. *Science Translational Medicine* 2013, **5**:181ra151.
6. **Kim H-Y**, Kasonde P, Mwiya M, Thea D, Kankasa C, Sinkala M, Aldrovandi G, Kuhn L: Pregnancy loss and role of infant HIV status on perinatal mortality among HIV-positive women. *BMC Pediatrics* 2012, **12:**138.
7. Bode L, Kuhn L, **Kim H-Y**, Hsiao L, Nissan C, Sinkala M, Kankasa C, Mwiya M, Thea DM, Aldrovandi GM: Human milk oligosaccharide concentration and risk of postnatal transmission of HIV through breastfeeding. *The American Journal of Clinical Nutrition* 2012, **96:**831-839.

MANUSCRIPTS UNDER REVIEW & PREPARATION

8. **Kim H-Y**, Grosso A, Ky-Zerbo O, Lougue M, Stahlman S, Samadoulougou C, Ouedraogo G, Kouanda S, Benjamin Liestman B, Baral S. Stigma as a barrier to healthcare utilization among men who have sex with men and female sex workers in Burkina Faso. *Annals of Epidemiology* 2016 [Under Review]
9. **Kim H-Y,** Hanrahan CF, Dowdy DW, Martinson NA, Golub J, Bridges JFP. Prioritizing maternal perceptions of preventive therapies for tuberculosis among HIV-positive pregnant women. *Int J Tuberc Lung Dis* 2016 [Under Review]

10. Hanrahan CF, **Kim H-Y,** Dowdy DW, Martinson NA, Golub J, Bridges JFP. Attribute development for best-worst scaling instruments: qualitative interviews to examine patients′ preferences of preventive therapies among HIV-positive people in South Africa.
11. Hanrahan CF, **Kim H-Y,** Dowdy DW, Martinson NA, Bridges JFP, Golub J. Patients′ preferences for provision of isoniazid preventive therapy among people living with HIV in South Africa.
12. **Kim H-Y,** Hanrahan CF, Dowdy DW, Martinson NA, Golub J, Bridges JFP. What motivates people newly diagnosed of HIV to take preventive therapies?: a conjoint analysis
13. **Kim H-Y,** Hanrahan CF, Dowdy DW, Martinson NA, Golub JFP. Cost-effectiveness of universal isoniazid preventive therapy among HIV-positive pregnant women.

PRESENTATIONS

ORAL: INVITED

2016 **Kim H-Y,** Hanrahan C, Dowdy DW, Chon S, Martinson N, Bridges JFP, Golub J. Perceived barriers and facilitators of isoniazid preventive therapy among HIV-positive people in South Africa. 46th Union World Conference on Lung Health. Liverpool, UK. October 2016.

ORAL: CONTRIBUTED

2016 Hojoon S, **Kim H-Y**, Lee S-H. The cost and cost-effectiveness of contact screening strategies amongst school children post TB outbreaks in Republic of Korea. The Korean Academy of Tuberculosis and Respiratory Diseases. Seoul, Korea. November 2016.

2016 Hanrahan CF, **Kim H-Y**, Dowdy D, K Mothloaleng, L Lebina, Martinson NA, Bridges JFP, Golub J. Patient preferences for provision of isoniazid preventive therapy among people living with HIV in South Africa. Oral abstract. 46th Union World Conference on Lung Health. Liverpool, UK. October 2016.

2011 Gray G, Violari A, **Kim H-Y**, Kuhn L, Goga A. Support for relactation among HIV-positive mothers: a pilot study in Soweto. 30th Conference on Priorities in Perinatal Care in Southern Africa. Polokwane, South Africa. March 2011.

POSTER

2016 **Kim H-Y,** Hanrahan C, Dowdy D, Chon Sandy, Martinson N, Bridges J, Golub J. Perceived barriers and facilitators of isoniazid preventive therapy among HIV-positive pregnant women in South Africa. TB2016. Durban, South Africa. July 2016.

2015 **Kim H-Y,** Grosso A, Ky-Zerbo O, Lougue M, Ouedraogo G, Kouanda S, Baral S. Stigma as barriers to healthcare among high risk groups for HIV transmission in Burkina Faso. 8th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention. Vancouver, Canada. July 2015.

2015 **Kim H-Y,** Dowdy DW, Martinson NA. Implementation of Male Circumcision for HIV Prevention. Global Health Day Poster Session, Baltimore, MD. April 2915.

2012 Kuhn L, **Kim H-Y**, Sinkala M, Mwiya M, Thea D, Kankasa C, Decker D, and Aldrovandi G**.** Safer weaning for HIV-positive women: influence of feeding behaviors

on breast milk HIV RNA and DNA concentrations. 19th Conference on Retroviruses and Opportunistic Infections. Seattle, WA. March 2012.

2012 **Kim H-Y**, Kuhn L, Aldrovandi G, Sinkala M, Kankasa C, Mwiya M, Thea D, Hsiao L, Nissan C, and Bode L. Breast milk oligosaccharides and postnatal HIV transmission. 19th Conference on Retroviruses and Opportunistic Infections. Seattle, WA. March 2012.

2012 **Kim H-Y,** Mwiya M, Kankasa C, Sinkala M, Kasonde P, Aldrovandi G, Thea D, Kuhn L. Role of infant HIV status in adverse pregnancy outcomes among HIV-positive women. 6th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention. Rome, Italy. July 2011.

TEACHING ASSISTANT

JOHNS HOPKINS SCHOOL OF PUBLIC HEALTH

2015 Epidemiologic Inference in Public Health 1
Instructor: David Celentano, PhD, Elizabeth Platz, PhD and Jennifer Deal, PhD
Methods and Applications of Cohort Studies, 2015 Summer Institute
Instructor: David W Dowdy, PhD, Keri Althoff , PhD and Hae-Young Kim**,** MPH
STATA Programming
Instructor: Dorry Segev, PhD and Allan Massie, PhD
Epidemiologic Methods 3
Instructor: David W Dowdy, MD PhD and Keri Althoff, PhD

2014 Epidemiologic Methods 2
Instructor: Gypsyamber D'Souza, PhD and Stephan Ehrhardt, PhD

ACTIVITIES

2014 - 2015	Service Chair, Epidemiology Student Organization Johns Hopkins Bloomberg School of Public Health
2014 - 2015	Infectious Disease Journal Club Coordinator Johns Hopkins Bloomberg School of Public Health
2014 – present	Afterschool School Program Coordinator Baltimore City Mission Center, Baltimore, MD

COMPUTING SKILLS

Statistical computing: SAS, STATA, R, Stella, SQL
Certified in Public Health by the National Board of Public Health Examiners